Exhibit 40

IARC MONOGRAPHS

ARSENIC, METALS, FIBRES, AND DUSTS

VOLUME 100 C
A REVIEW OF HUMAN CARCINOGENS

IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

International Agency for Research on Cancer
World Health Organization

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VOLUME 100 C
A REVIEW OF HUMAN CARCINOGENS

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 17-24 March 2009

LYON, FRANCE - 2012

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer
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IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed. The lists of IARC evaluations are regularly updated and are available on the Internet at http://monographs.iarc.fr/.

This programme has been supported since 1982 by Cooperative Agreement U01 CA33193 with the United States National Cancer Institute, Department of Health and Human Services. Additional support has been provided since 1986 by the Health, Safety and Hygiene at Work Unit of the European Commission Directorate-General for Employment, Social Affairs and Equal Opportunities, and since 1992 by the United States National Institute of Environmental Health Sciences, Department of Health and Human Services. The contents of this volume are solely the responsibility of the Working Group and do not necessarily represent the official views of the U.S. National Cancer Institute, the U.S. National Institute of Environmental Health Sciences, the U.S. Department of Health and Human Services, or the European Commission Directorate-General for Employment, Social Affairs and Equal Opportunities.

This volume was made possible, in part, through Cooperative Agreement CR 834012 with the United States Environmental Protection Agency, Office of Research and Development. The contents of this volume do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

Published by the International Agency for Research on Cancer,
150 cours Albert Thomas, 69372 Lyon Cedex 08, France

Distributed by WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland
(tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int).

IARC Library Cataloguing in Publication Data

A review of human carcinogens. Part C: Arsenic, metals, fibres, and dusts/ IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2009: Lyon, France)

(IARC monographs on the evaluation of carcinogenic risks to humans ; v. 100C)

1. Arsenic – adverse effects 2. Carcinogens 3. Dust – adverse effects
4. Metals – adverse effects 5. Mineral Fibres – adverse effects 4. Neoplasms – etiology
I. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans
II. Series

ISBN 978 92 832 1320 8 (NLM Classification: W1)
ISSN 1017-1606

PRINTED IN FRANCE

Lorenzo Tomatis (1929-2007)
Founder of the *IARC Monographs* Programme

Lorenzo Tomatis, MD, with other colleagues knowledgeable in primary prevention and environmental carcinogenesis, perceived in the 1960s the growing need to objectively evaluate carcinogenic risks by international groups of experts in chemical carcinogenesis. His vision and determination to provide a reliable source of knowledge and information on environmental and occupational causes of cancer led to his creating the *IARC Monographs* Programme for evaluating cancer risks to humans from exposures to chemicals. The first meeting, held in Geneva in December 1971, resulted in Volume 1 of the IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man [1972], a series known affectionately since as the "orange books". As a champion of chemical carcinogenesis bioassays, Tomatis defined and promoted the applicability and utility of experimental animal findings for identifying carcinogens and for preventing cancers in humans, especially in workers and children, and to eliminate inequalities in judging cancer risks between industrialized and developing countries. Tomatis' foresight, guidance, leadership, and staunch belief in primary prevention continued to influence the *IARC Monographs* as they expanded to encompass personal habits, as well as physical and biological agents. Lorenzo Tomatis had a distinguished career at the Agency, arriving in 1967 and heading the Unit of Chemical Carcinogenesis, before being Director from 1982 to 1993.

Volume 100 of the *IARC Monographs* Series is respectfully dedicated to him.

(photo: Roland Dray)

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NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean that an agent is capable of causing cancer. The *Monographs* evaluate cancer hazards, despite the historical presence of the word 'risks' in the title.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a *Monograph* does not mean that it is not carcinogenic. Similarly, identification of cancer sites with *sufficient evidence* or *limited evidence* in humans should not be viewed as precluding the possibility that an agent may cause cancer at other sites.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Section of IARC Monographs, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the *Monographs* as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Section of IARC Monographs, so that corrections can be reported in future volumes.

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PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a *Monograph* or list of evaluations.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended '...that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.' The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase 'of chemicals' was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Stewart & Kleihues, 2003). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad hoc Advisory Groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term 'agent' refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand as causation of, and susceptibility to, malignant disease become more fully understood.

A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

In the *Monographs*, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms 'neoplasm' and 'tumour' are used interchangeably.

The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006; see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged

on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme web site (http://monographs.iarc.fr). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate

or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section 4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) The Working Group

The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

(b) Invited Specialists

Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) Representatives of national and international health agencies

Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations.

(d) Observers with relevant scientific credentials

Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers from constituencies with differing perspectives. They are invited to observe the meeting and should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC Monographs* meetings (available at http://monographs.iarc.fr).

(e) The IARC Secretariat

The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano *et al.*, 2004).

The names and principal affiliations of participants are available on the *Monographs* programme web site (http://monographs.iarc.fr) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano *et al.*, 2005).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme web site (http://monographs.iarc.fr) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, before the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme web site soon after the meeting.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

Exposure data
Studies of cancer in humans
Studies of cancer in experimental animals
Mechanistic and other relevant data
Summary
Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

(a) General information on the agent

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

(b) Analysis and detection

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

(c) Production and use

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production, which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are

obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

(d) Occurrence and exposure

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described.

(e) Regulations and guidelines

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

(a) Types of study considered

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case–control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population

to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(b) Quality of studies considered

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to several aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

First, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Second, the authors should have taken into account — in the study design and analysis — other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than those with national rates. Internal comparisons of frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since they minimize the potential for

confounding related to the difference in risk factors between an external reference group and the study population.

Third, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(c) Meta-analyses and pooled analyses

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland, 1998).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(d) Temporal effects

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although, at best, they

allow only indirect inferences about mechanisms of carcinogenesis.

(e) Use of biomarkers in epidemiological studies

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio *et al.*, 1992; Toniolo *et al.*, 1997; Vineis *et al.*, 1999; Buffler *et al.*, 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(f) Criteria for causality

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

Several scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and coherence of the overall database are considered. Data on biomarkers may be employed

in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires first that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species (Wilbourn *et al.*, 1986; Tomatis *et al.*, 1989). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio *et al.*, 1995). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate

(e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

(a) Qualitative aspects

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence (Huff *et al.*, 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo

transition to malignancy, the agent should nevertheless be suspected of being carcinogenic and requires further investigation.

(b) Quantitative aspects

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce nonlinearity in the dose–response relationship (Hoel et al., 1983; Gart *et al.*, 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(c) Statistical analyses

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto *et al.*, 1980; Gart *et al.*, 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman *et al.*, 1994; Dunson *et al.*, 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls,

particularly when historical controls show high between-study variability and are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals (Haseman *et al.*, 1984; Fung *et al.*, 1996; Greim *et al.*, 2003).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

(a) Toxicokinetic data

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose–response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(b) Data on mechanisms of carcinogenesis

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells can be divided into three non-exclusive levels as described below.

(i) Changes in physiology

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

(ii) Functional changes at the cellular level

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related to the stimulation of DNA replication and transcription and changes in gap–junction-mediated intercellular communication.

(iii) Changes at the molecular level

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis (Vainio *et al.*, 1992; McGregor *et al.*, 1999). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system in vitro affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour promotion, cell transformation and gap–junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of

greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals in vivo indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated in vivo provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio *et al.*, 1992). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. Capen *et al.*, 1999).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(c) Other data relevant to mechanisms

A description is provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(d) Susceptibility data

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(e) Data on other adverse effects

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be found on the *Monographs* programme web site (http://monographs.iarc.fr).

(a) Exposure data

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(b) Cancer in humans

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(c) Cancer in experimental animals

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(d) Mechanistic and other relevant data

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and

the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

***Limited evidence of carcinogenicity*:** A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

***Inadequate evidence of carcinogenicity*:** The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

***Evidence suggesting lack of carcinogenicity*:** There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In

addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c) Mechanistic and other relevant data

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics,

physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as 'weak', 'moderate' or 'strong'. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is carcinogenic to humans.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental

animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is probably carcinogenic to humans.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is probably not carcinogenic to humans.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity*

in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

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GENERAL REMARKS

Part C of Volume 100 of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* contains updated assessments of arsenic, metals, fibres, and dusts that were first classified as *carcinogenic to humans (Group 1)* in Volumes 1–99.

Volume 100 – General Information

About half of the agents classified in Group 1 were last reviewed more than 20 years ago, before mechanistic studies became prominent in evaluations of carcinogenicity. In addition, more recent epidemiological studies and animal cancer bioassays have demonstrated that many cancer hazards reported in earlier studies were later observed in other organs or through different exposure scenarios. Much can be learned by updating the assessments of agents that are known to cause cancer in humans. Accordingly, IARC has selected *A Review of Human Carcinogens* to be the topic for Volume 100. It is hoped that this volume, by compiling the knowledge accumulated through several decades of cancer research, will stimulate cancer prevention activities worldwide, and will be a valued resource for future research to identify other agents suspected of causing cancer in humans.

Volume 100 was developed by six separate Working Groups:

Pharmaceuticals
Biological agents
Arsenic, metals, fibres, and dusts
Radiation
Personal habits and indoor combustions
Chemical agents and related occupations

Because the scope of Volume 100 is so broad, its *Monographs* are focused on key information. Each *Monograph* presents a description of a carcinogenic agent and how people are exposed, critical overviews of the epidemiological studies and animal cancer bioassays, and a concise review of the toxicokinetic properties of the agent, plausible mechanisms of carcinogenesis, and potentially susceptible populations, and life-stages. Details of the design and results of individual epidemiological studies and animal cancer bioassays are summarized in tables. Short tables that highlight key results appear in the printed version of Volume 100, and more extensive tables that include all studies appear on the website of the *IARC Monographs* programme (http://monographs.iarc.fr). For a few well-established associations (for example, tobacco smoke and human lung cancer), it was impractical to include all studies, even in the website tables. In those instances, the rationale for inclusion or exclusion of sets of studies is given.

Each section of Volume 100 was reviewed by a subgroup of the Working Group with appropriate subject expertise; then all sections of each *Monograph* were discussed together in a plenary session of the full Working Group. As a result, the evaluation statements and other conclusions reflect the views of the Working Group as a whole.

Volume 100 compiles information on tumour sites and mechanisms of carcinogenesis. This information will be used in two scientific publications that may be considered as annexes to this volume. One publication, *Tumour Site Concordance between Humans and Experimental Animals*, will analyse the correspondence of tumour sites among humans and different animal species. It will discuss the predictive value of different animal tumours for cancer in humans, and perhaps identify human tumour sites for which there are no good animal models. Another publication, *Mechanisms Involved in Human Carcinogenesis*, will describe mechanisms known to or likely to cause cancer in humans. Joint consideration of multiple agents that act through similar mechanisms should facilitate the development of a more comprehensive discussion of these mechanisms. Because susceptibility often has its basis in a mechanism, this could also facilitate a more confident and precise description of populations that may be susceptible to agents acting through each mechanism. This publication will also suggest biomarkers that could render future research more informative. In this way, IARC hopes that Volume 100 will serve to improve the design of future cancer studies.

Specific remarks about the review of the agents in this volume

1. Arsenic and metals

One issue for several of these agents was the designation of the agent classified as carcinogenic. Arsenic and the metals considered exist in several oxidation states and in different forms that have different chemical and physical properties: metallic/elemental forms, alloys, and multiple compounds. For arsenic and the metals, the Working Group needed to consider whether:

1) the metallic/elemental form itself is carcinogenic;
2) the metallic/elemental form and the compounds are carcinogenic; or
3) only certain compounds are carcinogenic.

The simultaneous review of arsenic and multiple metals in this volume offered the opportunity for the Working Group to address the designation of these elements and/or their compounds in a uniform fashion. There had been some lack of consistency in prior designations, in part reflecting the nature of the evidence available and precedents in terminology around specific elements. Arsenic, for example, is widely referred to as "arsenic" alone and not as "arsenic and arsenic compounds."

In the *Monograph* on nickel and nickel compounds, the Working Group phrased its evaluation of the epidemiological studies as "mixtures of nickel compounds and nickel metal." The overall evaluation, however, was constrained to cover only nickel compounds and not nickel metal, in accordance with IARC's previously announced plan that Volume 100 would evaluate agents that had been classified as *carcinogenic to humans (Group 1)* in Volumes 1–99, and only nickel compounds had been classified in Group 1 in Volume 49 (IARC, 1990). Based on the previous evaluation in Volume 49, nickel metal remains classified as *possibly carcinogenic to humans (Group 2B)*. The Working Group

recommends that there is a need for IARC to re-evaluate nickel metal in the near future in the context of the review of nickel compounds in this volume.

The situation was similar for chromium in that the review in Volume 100 considered the carcinogenicity of chromium (VI), but not of chromium with other oxidation states. The decision to omit metallic chromium or chromium (III) compounds from present assessment should not be interpreted as implying that these compounds are not carcinogenic or that the current evidence base is unchanged from that at the time of Volume 49 (IARC, 1990). Indeed, the evidence base has expanded and the Working Group does not pre-judge what the results of a new evaluation might be.

In the *Monograph* on arsenic and arsenic compounds, the Working Group developed a single updated assessment of agents that had been evaluated in previous *Monograph*s on arsenic and arsenic compounds (Volume 23 and Supplement 7, IARC, 1980, 1987a), arsenic in drinking-water (Volume 84, IARC, 2004), and gallium arsenide (Volume 86, IARC, 2006). It should be understood that arsenic in drinking-water and gallium arsenide should continue to be regarded as *carcinogenic to humans*, covered in this volume by the evaluation of arsenic and inorganic arsenic compounds.

In interpreting the human evidence on these agents, a particular difficulty was posed by the mixed exposures sustained by the worker populations included in the cohort studies. For groups exposed simultaneously to an agent in elemental/metallic form and to its compounds, the evidence may be uninformative as to the components of the mixture that cause cancer. When the evidence comes only from mixed exposure circumstances, the Working Group considered that the evaluation should be phrased as referring to "exposure to the element and its compounds."

This phrasing should not be interpreted as meaning that:

1) separate human evidence is available for the metallic/elemental form itself and for each of its compounds or

2) the evaluation of human evidence applies separately to the metallic/elemental form and to each of its compounds.

From the human evidence, insight can be gained as to the specific carcinogenic agent if sufficient informative studies are available on multiple cohorts having exposures to differing speciations of the element. Additionally, cancer bioassay and mechanistic evidence are critical to determining which components of the exposure mixture are carcinogenic, and were given full consideration by the Working Group.

2. Fibres and Dusts

When an agent is referred to as a dust, the assumption made by the Working Group was that the major route of exposure was by inhalation.

The assessment of toxicity and carcinogenicity of poorly soluble materials in the form of particles or fibres is difficult for the following reasons:

First, chemical composition alone does not fully define the relevant biological properties of particulate materials.

Second, particulate and fibrous carcinogens may undergo more complex metabolic transformation than other chemical agents. The surface of dusts may be modified *in vivo*, for example, there may be removal or deposition of metal ions or protein adsorption. These *in vivo* modifications may alter potency of the native particles or fibres.

Third, when comparing potency of dust particles, surface area may be a more appropriate dose metric than mass. In many cases, the extent of particle-derived free radicals and release of inflammatory mediators and the subsequent biological response correlate with surface area.

Fourth, particles and fibres with low solubility including quartz and asbestos fibres induce toxicity in the particulate form and not as individual molecules or ions. Particles and fibres may be deposited and retained in a focal area for a long time and contribute to the induction of lesions at this site. Particles and fibres may also be translocated to extrapulmonary sites.

Two occupations previously classified in Group 1 are considered in this volume. Boot and shoe manufacture and repair was previously evaluated in Volume 25 and in Supplement 7 (IARC, 1981, 1987a). In this volume, the Working Group concluded that the nasal sinus tumours and leukaemias observed in the epidemiological studies could be attributed to exposure to leather dust and to benzene, respectively. In accordance with the Preamble (see part B, Section 6a), the Working Group focused its evaluation more narrowly on leather dust, after searching for other studies involving this new agent. The Working Group renamed this *Monograph* "Leather Dust." (The *Monograph* on Benzene will be updated in Part F of Volume 100.)

Furniture and cabinet making was also previously evaluated in Volume 25 and in Supplement 7 (IARC, 1981, 1987a). In this volume, the Working Group concluded that the tumours of the nasal sinus and nasopharynx observed in the epidemiological studies could be attributed to exposure to wood dust or formaldehyde. Accordingly, these studies are reviewed in this volume in the *Monograph* on Wood Dust. (The *Monograph* on Formaldehyde will also be updated in Part F of Volume 100.)

The previous *IARC Monographs* on Talc Containing Asbestiform Fibres (Volume 42 and Supplement 7, IARC, 1987a, b) concerned talc described as containing asbestiform tremolite and anthophyllite. These fibres fit the definition of asbestos and therefore a separate review of talc containing asbestiform fibres was not undertaken. The studies on talc containing asbestiform fibres were considered when developing the *Monograph* on asbestos. Talc containing asbestos as well as other mixtures containing asbestos should be regarded as *carcinogenic to humans*.

In evaluating the carcinogenicity of asbestos fibres, the Working Group evaluated experimental data using the six types of asbestos fibres (Chrysotile, Amosite, Crocidolite, Tremolite, Actinolite and Anthophyllite) and erionite based on *in vitro* cellular assays and/or cancer bioassays. It should be understood that minerals containing asbestos in any form should be regarded as *carcinogenic to humans*. The Working Group agreed that the most important physicochemical properties of asbestos fibres relevant for toxicity and carcinogenicity are surface chemistry and reactivity, surface area, fibre dimensions, and biopersistence. Extrapolation of toxicity to other crystalline mineral fibres should not be done in the absence of epidemiological or experimental data based on *in vitro* and *in vivo* assays.

The toxicity of crystalline silica dusts obtained from different sources may be related to their geological history, process of particle formation, modifications during mining, processing and use, or surface contaminants even in trace amounts. Freshly ground crystalline silica exhibits a higher toxic potential than aged dusts. Crystalline silica may occur embedded in clays and other minerals or may be mixed with other materials in commercial products. It is possible that these other minerals or materials may adsorb onto the surface of crystalline silica dust and modify its reactivity. However, the extent of surface coverage and the potency of these modified dusts after residence in the lungs have not been systematically assessed.

3. Cross-cutting issues

3.1 Epidemiology

The epidemiological evidence considered in this Volume largely comes from studies of worker groups exposed to the agents under consideration. Additionally, population-based case–control studies also supply relevant evidence as do a few case series. There are several general issues related to these lines of epidemiological evidence that are covered in these comments.

The epidemiological evidence considered in this Volume largely comes from studies of worker groups exposed to the agents under consideration at levels that were high in relation to contemporary exposures, particularly in more developed countries. The cohort studies of workers have the general design of longitudinal follow-up of groups known to be exposed to the agent of interest in their workplace. Some cohort studies incorporate specific, unexposed comparison populations whereas others make a comparison to the rates of mortality in the general population, typically at the national level but sometimes on smaller geographic domains, e.g. states or counties. The measures of association used (e.g. standardized mortality ratios or SMRs) compare the rate of outcome in the exposed population to that in the unexposed population. One general concern in interpreting these measures of association is the appropriateness of the comparison population selected. National rates are often used because they are available and stable, but use of such rates may be inappropriate if there are important differences between the study population and the population at large on factors that might confound or modify the relationship between exposure and outcome. With appropriate consideration, local rates may be more suitable because factors that may confound the relationship between cancer risk and exposure, e.g. cigarette smoking, are likely to be more similar than a national population to the distributions in the worker population. Use of both national and local rates provides a sensitivity analysis as to the potential role of confounding. However, use of local rates may introduce bias if they are influenced by occupational or environmental exposures resulting from the plants under study, or if the geographical areas available for analyses do not reflect the areas from which the occupational population as drawn. Use of local rates may also result in imprecision of the epidemiological risk estimate due to instability resulting from small numbers and/or inaccuracies in small area data. The most appropriate comparison group would be other worker populations.

The informativeness of a cohort study depends on its size, i.e. the numbers of participants and outcome events. The sample sizes of the various cohort studies reflect the numbers of workers employed during the period of interest. Many of the studies had small population sizes, leading to imprecise measures of association, i.e. with wide confidence intervals. For some agents, small studies were set aside because they were uninformative. The Working Group did not attempt to combine the results of all studies, regardless of size, using quantitative meta-analysis.

3.2 Mixed exposures

In many of the cohorts studied, the workers were exposed to mixtures generated by industrial processes that contained not only the agent(s) of concern, but other potentially carcinogenic agents as well. For example, in some populations exposed to chromium, there was simultaneous exposure to arsenic. In analyses of the data from such studies, efforts were made to separate the effect of the agent of concern from the effects of other, potentially confounding agents. Such disentanglement is

possible only if the exposures are not highly correlated and the requisite data on exposures to the agents are available. There is also the assumption underlying such analyses that the effects of the various agents in the mixture are independent. In its deliberations, the Working Group recognized that exposures to many of the agents took place through exposures to mixtures containing them and took this into account in its interpretation of the evidence.

Exposures were estimated for study participants using approaches that typically were based on measurements and reconstruction of exposures based on work history and job–exposure matrices. Additionally, duration of employment was used as a surrogate for exposure. The measures of exposure were used in analyses directed at characterizing exposure–response relationships. Given the limited data available for estimating exposures, the exposure measures were subject to some degree of misclassification, likely random. One consequence of such exposure misclassification would be a blunting of estimated exposure–response relationships.

3.3 Smoking as confounder

In interpreting findings related to lung cancer and other sites for which smoking is a cause, there is the potential for confounding by smoking, particularly because many studies lacked information on smoking and direct adjustment for smoking was not possible. In assessing the potential for confounding by smoking, consideration was given to whether internal comparisons were made, which should not be as likely to be confounded as external comparisons. Additionally, some studies used available smoking information to estimate the potential for confounding by smoking. Such analyses are useful but have the underlying assumption that the effects of smoking and the agent of interest are independent.

Since the prior reviews, several data sets had undergone re-analysis by analysts who were not the original investigators. As appropriate, the Working Group considered these re-analyses to assess any insights into the original analyses.

A summary of the findings of this volume appears in The Lancet Oncology (Straif et al., 2009).

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ARSENIC AND ARSENIC COMPOUNDS

Arsenic and arsenic compounds were considered by previous IARC Working Groups in 1979, 1987, and 2002 (IARC, 1980, 1987, 2004). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Information on the physical and chemical properties of arsenic and arsenic compounds can be found in Table 1.1, for further details please refer to IARC (1980). The list is not exhaustive, nor does it comprise necessarily the most commercially important arsenic-containing substances; rather, it indicates the range of arsenic compounds available.

1.2 Chemical and physical properties of the agents

Arsenic (atomic number, 33; relative atomic mass, 74.92) has chemical and physical properties intermediate between a metal and a non-metal, and is often referred to as a metalloid or semi-metal. It belongs to Group VA of the Periodic Table, and can exist in four oxidation states: –3, 0, +3, and +5. Arsenite, As^{III}, and arsenate, As^{V}, are the predominant oxidation states under, respectively, reducing and oxygenated conditions (WHO, 2001; IARC, 2004).

From a biological and toxicological perspective, there are three major groups of arsenic compounds:

-inorganic arsenic compounds,
-organic arsenic compounds, and
-arsine gas.

Of the inorganic arsenic compounds, arsenic trioxide, sodium arsenite and arsenic trichloride are the most common trivalent compounds, and arsenic pentoxide, arsenic acid and arsenates (e.g. lead arsenate and calcium arsenate) are the most common pentavalent compounds. Common organic arsenic compounds include arsanilic acid, methylarsonic acid, dimethylarsinic acid (cacodylic acid), and arsenobetaine (WHO, 2000).

1.3 Use of the agents

Arsenic and arsenic compounds have been produced and used commercially for centuries. Current and historical uses of arsenic include pharmaceuticals, wood preservatives, agricultural chemicals, and applications in the mining, metallurgical, glass-making, and semiconductor industries.

Arsenic was used in some medicinal applications until the 1970s. Inorganic arsenic was used

Table 1.1 Chemical names, CAS numbers, synonyms, and molecular formulae of arsenic and arsenic compounds

Chemical name	CAS Reg. No.	Synonyms	Formula
Arsanilic acid	98-50-0	Arsonic acid, (4-aminophenyl)-	$C_6H_8AsNO_3$
Arsenic[a]	7440-38-2	Metallic arsenic	As
Arsenic(V) pentoxide[b]	1303-28-2	Arsenic oxide [As_2O_5]	As_2O_5
Arsenic(III) sulfide	1303-33-9	Arsenic sulfide [As_2S_3]	As_2S_3
Arsenic(III) trichloride	7784-34-1	Arsenic chloride [$AsCl_3$]	$AsCl_3$
Arsenic(III) trioxide[a,c]	1327-53-3	Arsenic oxide [As_2O_3]	As_2O_3
Arsenobetaine	64436-13-1	Arsonium, (carboxymethyl) trimethyl-, hydroxide, inner salt; 2-(trimethylarsonio)acetate	$C_5H_{11}AsO_2$
Arsine	7784-42-1	Arsenic hydride	AsH_3
Calcium arsenate	7778-44-1	Arsenic acid [H_3AsO_4] calcium salt (2:3)	$(AsO_4)_2.3Ca$
Dimethylarsinic acid	75-60-5	Cacodylic acid	$C_2H_7AsO_2$
Lead arsenate	7784-40-9	Arsenic acid [H_3AsO_4], lead (2+) salt (1:1)	$HAsO_4.Pb$
Methanearsonic acid, disodium salt	144-21-8	Arsonic acid, methyl-, disodium salt	$CH_3AsO_3.2Na$
Methanearsonic acid, monosodium salt	2163-80-6	Arsonic acid, methyl-, monosodium salt	$CH_4AsO_3.Na$
Potassium arsenate[d]	7784-41-0	Arsenic acid [H_3AsO_4], monopotassium salt	$H_2AsO_4.K$
Potassium arsenite	13464-35-2	Arsenous acid, potassium salt	$AsO_2.K$
Sodium arsenate[e]	7631-89-2	Arsenic acid, [H_3AsO_4], monosodium salt	$H_2AsO_4.Na$
Sodium arsenite	7784-46-5	Arsenous acid, sodium salt	$AsO_2.Na$
Sodium cacodylate	124-65-2	Arsinic acid, dimethyl-, sodium salt	$C_2H_6AsO_2.Na$

[a] As_2O_3 is sometimes erroneously called 'arsenic'.
[b] The name 'arsenic acid' is commonly used for As_2O_5 as well as for the various hydrated products (H_3AsO_4, $H_4As_2O_7$).
[c] As_2O_3 is sometimes called 'arsenic oxide', but this name is more properly used for As_2O_5.
[d] The other salts, K_3AsO_4 and K_2HAsO_4, do not appear to be produced commercially.
[e] The name 'sodium arsenate' is also applied to both the disodium [7778-43-0] and the trisodium [13464-38-5] salts; it is therefore not always possible to determine which substance is under discussion.

in the treatment of leukaemia, psoriasis, and chronic bronchial asthma, and organic arsenic was used in antibiotics for the treatment of spirochetal and protozoal disease (ATSDR, 2007).

Inorganic arsenic is an active component of chromated copper arsenate, an antifungal wood preservative used to make "pressure-treated" wood for outdoor applications. Chromated copper arsenate is no longer used in residential applications, following a voluntary ban on its use in Canada and the United States of America at the end of 2003.

In the agricultural industry, arsenic has historically been used in a range of applications, including pesticides, herbicides, insecticides, cotton desiccants, defoliants, and soil sterilants. Inorganic arsenic pesticides have not been used for agricultural purposes in the USA since 1993. Organic forms of arsenic were constituents of some agricultural pesticides in the USA. However, in 2009, the US Environmental Protection Agency issued a cancellation order to eliminate and phase out the use of organic arsenical pesticides by 2013 (EPA, 2009). The one exception to the order is monosodium methanearsonate (MSMA), a broadleaf weed herbicide, which will continue to be approved for use on cotton. Small amounts of disodium methanearsonate (DSMA, or cacodylic acid) were historically applied to cotton fields as herbicides, but its use is now prohibited under the aforementioned US EPA 2009 organic arsenical product cancellation. Other organic

arsenicals (e.g. roxarsone, arsanilic acid and its derivatives) are used as feed additives for poultry and swine to increase the rate of weight gain, to improve feed efficiencies, pigmentation, and disease treatment and prevention (EPA, 2000, 2006; FDA, 2008a, b).

Arsenic and arsenic compounds are used for a variety of other industrial purposes. Elemental arsenic is used in the manufacture of alloys, particularly with lead (e.g. in lead acid batteries) and copper. Gallium arsenide and arsine are widely used in the semiconductor and electronics industries. Because of its high electron mobility, as well as light-emitting, electromagnetic and photovoltaic properties, gallium arsenide is used in high-speed semiconductor devices, high-power microwave and millimetre-wave devices, and opto-electronic devices, including fibre-optic sources and detectors (IARC, 2006). Arsine is used as a doping agent to manufacture crystals for computer chips and fibre optics.

Arsenic and arsenic compounds are used in the manufacture of pigments, sheep-dips, leather preservatives, and poisonous baits. They are also used in catalysts, pyrotechnics, antifouling agents in paints, pharmaceutical substances, dyes and soaps, ceramics, alloys (automotive solder and radiators), and electrophotography.

Historically, the USA has been the world's largest consumer of arsenic. Prior to 2004, about 90% of the arsenic consumed, as arsenic trioxide, was in the manufacture of wood preservatives. Since the voluntary ban on chromated copper arsenate in residential applications came into effect at the end of 2003, the consumption of arsenic for wood preservation has declined, dropping to 50% in 2007 (USGS, 2008). During 1990–2002, approximately 4% of arsenic produced was used in the manufacture of glass, and 1–4% was used in the production of non-ferrous alloys (NTP, 2005).

1.4 Environmental occurrence

Arsenic is the 20th most common element in the earth's crust, and is emitted to the environment as a result of volcanic activity and industrial activities. Mining, smelting of non-ferrous metals and burning of fossil fuels are the major anthropogenic sources of arsenic contamination of air, water, and soil (primarily in the form of arsenic trioxide). The historical use of arsenic-containing pesticides has left large tracts of agricultural land contaminated. The use of arsenic in the preservation of timber has also led to contamination of the environment (WHO, 2000, 2001).

1.4.1 Natural occurrence

In nature, arsenic occurs primarily in its sulfide form in complex minerals containing silver, lead, copper, nickel, antimony, cobalt, and iron. Arsenic is present in more than 200 mineral species, the most common of which is arsenopyrite. Terrestrial abundance of arsenic is approximately 5 mg/kg, although higher concentrations are associated with sulfide deposits. Sedimentary iron and manganese ores as well as phosphate-rock deposits occasionally contain levels of arsenic up to 2900 mg/kg (WHO, 2001).

1.4.2 Air

Arsenic is emitted to the atmosphere from both natural and anthropogenic sources. Approximately one-third of the global atmospheric flux of arsenic is estimated to be from natural sources (7900 tonnes per year). Volcanic activity is the most important natural contributor, followed by low-temperature volatilization, exudates from vegetation, and windblown dusts. Anthropogenic sources are estimated to account for nearly 24000 tonnes of arsenic emitted to the global atmosphere per year. These emissions arise from the mining and smelting of base metals, fuel combustion (e.g. waste and low-grade brown

coal), and the use of arsenic-based pesticides (WHO, 2000, 2001).

Arsenic is present in the air of suburban, urban, and industrial areas mainly as inorganic particulate (a variable mixture of As^{III} and As^{V}, with the pentavalent form predominating). Methylated arsenic is assumed to be a minor component of atmospheric arsenic (WHO, 2000). Mean total arsenic concentrations in air range from 0.02–4 ng/m^3 in remote and rural areas, and from 3–200 ng/m^3 in urban areas. Much higher concentrations (> 1000 ng/m^3) have been measured in the vicinity of industrial sources, such as non-ferrous metal smelters, and arsenic-rich coal-burning power plants (WHO, 2001).

1.4.3 Water

Arsenic, from both natural and anthropogenic sources, is mainly transported in the environment by water. The form and concentration of arsenic depends on several factors, including whether the water is oxygenated (for example, arsenites predominate under reducing conditions such as those found in deep well-waters), the degree of biological activity (which is associated with the conversion of inorganic arsenic to methylated arsenic acids), the type of water source (for example, open ocean seawater versus surface freshwater versus groundwater), and the proximity of the water source to arsenic-rich geological formations and other anthropogenic sources (WHO, 2000, 2001).

The concentration of arsenic in surface freshwater sources, like rivers and lakes, is typically less than 10 µg/L, although it can be as high as 5 mg/L near anthropogenic sources. Concentrations of arsenic in open ocean seawater and groundwater average 1–2 µg/L, although groundwater concentrations can be up to 3 mg/L in areas with volcanic rock and sulfide mineral deposits (WHO, 2001).

Exposure to high levels of arsenic in drinking-water has been recognized for many decades in some regions of the world, notably in the People's Republic of China, Taiwan (China), and some countries in Central and South America. More recently, several other regions have reported having drinking-water that is highly contaminated with arsenic. In most of these regions, the drinking-water source is groundwater, naturally contaminated from arsenic-rich geological formations. The primary regions where high concentrations of arsenic have been measured in drinking-water include large areas of Bangladesh, China, West Bengal (India), and smaller areas of Argentina, Australia, Chile, Mexico, Taiwan (China), the USA, and Viet Nam. In some areas of Japan, Mexico, Thailand, Brazil, Australia, and the USA, mining, smelting and other industrial activities have contributed to elevated concentrations of arsenic in local water sources (IARC, 2004).

Levels of arsenic in affected areas may range from tens to hundreds or even thousands of micrograms per litre, whereas in unaffected areas, levels are typically only a few micrograms per litre. Arsenic occurs in drinking-water primarily as As^{V}, although in reducing environments significant concentrations of As^{III} have also been reported. Trace amounts of methylated arsenic species are typically found in drinking-water, and higher levels are found in biological systems. More complete data on arsenic in water may be found in the previous *IARC Monograph* (IARC, 2004).

1.4.4 Soil and sediments

Natural and anthropogenic sources contribute to the levels of arsenic found in soil and sediments. Mean background concentrations in soil are often around 5 mg/kg, but can range from as low as 1 mg/kg to as high as 40 mg/kg. This variation in levels of naturally occurring arsenic in soils is associated with the presence of geological formations (e.g. sulfide ores, mineral sediments beneath peat bogs). Soils contaminated with arsenic from anthropogenic sources (e.g. mine/

smelter wastes, agricultural land treated with arsenical pesticides) can have concentrations of arsenic up to several grams per kilogram. Mean sediment arsenic concentrations range from 5–3000 mg/kg, with the higher levels occurring in areas of anthropogenic contamination (WHO, 2001).

1.5 Human exposure

1.5.1 Exposure of the general population

The primary route of arsenic exposure for the general population is via the ingestion of contaminated food or water. The daily intake of total arsenic from food and beverages is generally in the range of 20–300 µg/day.

Inhalation of arsenic from ambient air is generally a minor exposure route for the general population. Assuming a breathing rate of 20 m^3/day, the estimated daily intake may amount to about 20–200 ng in rural areas, 400–600 ng in cities without substantial industrial emission of arsenic, about 1 µg/day in a non-smoker and more in polluted areas, and up to approximately 10 µg/day in a smoker (WHO, 2000, 2001).

1.5.2 Occupational exposure

Inhalation of arsenic-containing particulates is the primary route of occupational exposure, but ingestion and dermal exposure may be significant in particular situations (e.g. during preparation of timber treated with chromated copper arsenate). Historically, the greatest occupational exposure to arsenic occurred in the smelting of non-ferrous metal, in which arseniferous ores are commonly used. Other industries or industrial activities where workers are or were exposed to arsenic include: coal-fired power plants, battery assembly, preparation of or work with pressure-treated wood, glass-manufacturing, and the electronics industry. Estimates of the number of workers potentially exposed to arsenic and arsenic compounds have been developed by the NIOSH in the USA and by CAREX in Europe. Based on the National Occupation Exposure Survey (NOES), conducted during 1981–83, NIOSH estimated that 70000 workers, including approximately 16000 female workers, were potentially exposed to arsenic and arsenic compounds in the workplace (NIOSH, 1990). Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX (CARcinogen EXposure) database estimated that 147569 workers were exposed to arsenic and arsenic compounds in the European Union, with over 50% of workers employed in the non-ferrous base metal industries (n = 40426), manufacture of wood and wood and cork products except furniture (n = 33959), and construction (n = 14740). CAREX Canada estimates that 25000 Canadians are exposed to arsenic in their workplaces (CAREX Canada, 2011). These industries include: sawmills and wood preservation, construction, farms, non-ferrous metal (except aluminium) production and processing, iron and steel mills and ferro-alloy manufacturing, oil and gas extraction, metal ore mining, glass and glass-product manufacturing, semiconductor manufacturing, and basic chemical manufacturing.

1.5.3 Dietary exposure

Low levels of inorganic and organic arsenic have been measured in most foodstuffs (typical concentrations are less than 0.25 mg/kg). Factors influencing the total concentration of arsenic in food include: food type (e.g. seafood versus meat or dairy), growing conditions (e.g. soil type, water, use of arsenic-containing pesticides), and food-processing techniques. The highest concentrations of arsenic have been found in seafood (2.4–16.7 mg/kg in marine fish, 3.5 mg/kg in mussels, and more than 100 mg/kg in certain crustaceans), followed by meats, cereals, vegetables, fruit, and dairy products. Inorganic arsenic

is the predominant form found in meats, poultry, dairy products and cereal, and organic arsenic (e.g. arsenobetaine) predominates in seafood, fruit, and vegetables (WHO, 2000, 2001).

Regional differences are seen in the daily intake of total arsenic through food, and are mainly attributable to variations in the quantity of seafood consumed. For example, the daily dietary intake of total arsenic in Japan is higher than that in Europe and the USA (WHO, 2000). Based on the limited data available, it is estimated that approximately 25% of daily dietary arsenic intake is from inorganic sources. Arsenic intake is typically higher in men than it is in women and children, with estimated levels ranging from 1.3 µg/day for infants under 1 year of age, 4.4 µg/day for 2-year olds, 9.9 µg/day for 25–30-year-old men, 10 µg/day for 60–65-year-old women, and 13 µg/day for 60–65-year-old men (WHO, 2001).

1.5.4 Biomarkers of exposure

Arsine generation atomic absorption spectrometry (AAS) is the method of choice for biological monitoring of exposure to inorganic arsenic (WHO, 2000). The absorbed dose of arsenic can be identified and quantified in hair, nail, blood or urine samples. Because arsenic accumulates in keratin-rich tissue, total arsenic levels in hair, fingernails or toenails are used as indicators of past exposures. In contrast, because of its rapid clearing and metabolism, blood arsenic, urine arsenic, and urine arsenic metabolites (inorganic arsenic, monomethylarsonic acid [MMA^V] and dimethylarsinic acid [DMA^V]) are typically used as indicators of recent exposure.

The concentration of metabolites of inorganic arsenic in urine generally ranges from 5–20 µg/L, but may exceed 1000 µg/L (WHO, 2001). Time-weighted average (TWA) occupational exposure to airborne arsenic trioxide is significantly correlated with the inorganic arsenic metabolites in urine collected immediately after a shift or just before the next shift. For example, at an airborne concentration of 50 µg/m^3, the mean concentration of arsenic derived from the sum of the three inorganic arsenic metabolites in a post-shift urine sample was 55 µg/g of creatinine. In non-occupationally exposed subjects, the sum of the concentration of the three metabolites in urine is usually less than 10 µg/g of creatinine (WHO, 2000).

2. Cancer in Humans

The epidemiological evidence on arsenic and cancer risk comes from two distinct lines of population studies, characterized by the medium of exposure to arsenic. One set of studies addresses the cancer risk associated with inhalation. These studies involve populations that are largely worker groups who inhaled air contaminated by arsenic and other agents, as a consequence of various industrial processes. The second set of studies was carried out in locations where people ingested arsenic in drinking-water at high concentrations over prolonged periods of time.

2.1 Types of human exposure circumstances studied

2.1.1 Arsenic exposure by inhalation

The cohort studies and nested case–control studies considered in this *Monograph* that are relevant to airborne arsenic include workers in metal smelters and refineries, and miners of various ores. Case–control studies within the general population addressed occupational exposures more generally. Consequently, the exposure to inhaled arsenic was accompanied by exposures to other potentially toxic and carcinogenic by-products of combustion, such as sulfur oxides with copper smelting, polycyclic aromatic hydrocarbons, and particulate matter.

Most studies did not attempt to estimate separately exposures to the full set of agents in the inhaled mixtures, leaving open the possibility of some confounding or modification of the effect of arsenic by synergistic interactions.

2.1.2 Arsenic exposure by ingestion

For most human carcinogens, the major source of evidence contributing to causal inferences arises from case–control and cohort studies. In contrast, for arsenic in drinking-water, ecological studies provide important information on causal inference, because of the large exposure contrasts and the limited population migration. For arsenic, ecological estimates of relative risk are often so high that potential confounding with known causal factors could not explain the results. Although food may also be a source of some ingested arsenic, in several regions of the world where the concentrations of arsenic in drinking-water is very high, arsenic intake through food consumption contributes a relatively small cancer risk to the local residents (Liu *et al.*, 2006a).

The strongest evidence for the association of human cancer with arsenic in drinking-water comes from studies in five areas of the world with especially elevated levels of naturally occurring arsenic: south-western and north-eastern Taiwan (China), northern Chile, Cordoba Province in Argentina, Bengladesh, West Bengal (India), and other regions in the Ganga plain. Although data contributing to our understanding also come from many other places, the current review is largely restricted to the major studies from these regions. Some of the oral exposure may occur via seafood. However, no epidemiological studies were available with regard to the cancer risk associated with arsenic exposure via seafood, in which arsenic may occur as particular organic compounds such as arsenobetaine and arsenocholine.

(a) Taiwan (China)

Exposure to arsenic was endemic in two areas of Taiwan (China): The south-western coastal area (Chen *et al.*, 1985), and the north-eastern Lanyang Basin (Chiou *et al.*, 2001). Residents in the south-western areas drank artesian well-water with high concentrations of arsenic from the early 1910s to the late 1970s, with levels mostly above 100 µg/L (Kuo, 1968; Tseng *et al.*, 1968). In the Lanyang Basin, residents used arsenic-contaminated water from household tube wells starting in the late 1940s. Arsenic in the water of 3901 wells, tested in 1991–94 ranged from undetectable (< 0.15 µg/L) to 3.59 mg/L (median = 27.3 µg/L) (Chiou *et al.*, 2001).

(b) Northern Chile

The population-weighted average concentration of arsenic in drinking-water in Region II, an arid region of northern Chile, was about 570 µg/L over 15 years (1955–69) (Smith *et al.*, 1998). With the introduction of a water-treatment plant in 1970, levels decreased. By the late 1980s, arsenic levels in drinking-water had decreased to less than 100 µg/L in most places. With minor exceptions, water sources elsewhere in Chile have had low concentrations of arsenic (less than 10 µg/L) (Marshall *et al.*, 2007).

(c) Cordoba Province, Argentina

Of the 24 counties in Cordoba Province, two have been characterized as having elevated exposure to arsenic in drinking-water (average level, 178 µg/L), six as having medium exposure, and the remaining 16 rural counties as having low exposure (Hopenhayn-Rich *et al.*, 1996, 1998).

(d) Bangladesh, West Bengal (India), and other locations in the Ganga plain

Millions of tube wells were installed in West Bengal (India), Bangladesh, and other regions in the Ganga plain of India and Nepal starting in the late 1970s to prevent morbidity and mortality

from gastrointestinal disease (Smith *et al.*, 2000). Elevated arsenic in wells in Bangladesh was confirmed in 1993 (Khan *et al.*, 1997). In a Bangladesh survey by the British Geological Survey of 2022 water samples in 41 districts, 35% were found to have arsenic levels above 50 µg/L, and 8.4% were above 300 µg/L, with an estimate of about 21 million persons exposed to arsenic concentrations above 50 µg/L (Smith *et al.*, 2000).

2.2 Cancer of the lung

2.2.1 Exposure via inhalation

Several ecological studies were conducted on populations exposed to arsenic through industrial emissions. The worker studies primarily provide information on lung cancer. The case–control studies are also mostly directed at lung cancer, with one on non-melanoma skin cancer (see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.1.pdf).

The cohort studies reviewed previously and here consistently show elevated lung cancer risk in the various arsenic-exposed cohorts compared with the general population or other comparison groups, with most values in the range of 2–3 (see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.2.pdf and Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.3.pdf).

The studies incorporate diverse qualitative and quantitative indices of exposure that include measures of average airborne concentration of exposure, cumulative exposure across the work experience, and duration of exposure. There is consistent evidence for a positive exposure–response relationship between the indicators of exposure and lung cancer risk. Case–control studies nested within occupational cohorts provided similar evidence with regard to exposure–response relationships.

Several analyses further explored the relationship between arsenic exposure and lung cancer risk using models based on either empirical, i.e. descriptive, or biological data (see Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.4.pdf).

Using data from the Tacoma, Washington smelter workers, Enterline *et al.* (1987) modelled the relationship between lung cancer risk and airborne arsenic exposure using power functions, and found that the exposure–response relationship was steeper at lower concentrations than shown in conventional analyses, and was concave downwards at higher concentrations. By contrast, the relationship of risk with urine arsenic concentration was linear. Lubin *et al.* (2000, 2008) analysed the exposure–response relationship of lung cancer risk with arsenic exposure in the cohort of Montana smelter workers, now followed for over 50 years. Overall, a linear relationship of risk with cumulative exposure was found; however, the slope of the relationship increased with the average concentration at which exposure had taken place, that is, the effect of a particular cumulative exposure was greater if received at a faster rate.

For a comparison of the different studies, see Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.5.pdf.

2.2.2 Exposure via ingestion

A summary of the findings of epidemiological studies on arsenic in drinking-water and risk for lung cancer are shown in Table 2.6 (water exposures) available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.6.pdf, and online Tables 2.1 to 2.4 (air exposures).

(a) Ecological studies

Ecological studies, based on mortality records, were conducted in the arseniasis endemic area of south-western Taiwan (China) (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Tsai *et al.*, 1999). All studies found elevated risks for lung cancer mortality associated with levels of arsenic in drinking-water, or surrogate measurements.

In Chile, Rivara *et al.* (1997) found an elevated relative risk (RR) for mortality from lung cancer in 1976–92 in Region II compared with Region VIII, a low-exposure area. Smith *et al.* (1998) found an elevated standardized mortality ratio (SMR) of approximately 3 for lung cancer for both sexes in Region II, using the national rate as standard. In Cordoba Province, Argentina, significant increases in lung cancer mortality were associated with increasing exposure to arsenic (Hopenhayn-Rich *et al.*, 1998). Smith *et al.* (2006) found an elevated lung cancer mortality (RR, 7.0; 95%CI: 5.4–8.9) among the 30–49-year-old residents of Antofagasta and Mejillones born in the period 1950–57, just before the period of exposure to high arsenic levels (1958–70). They were exposed in early childhood to high levels of arsenic through the drinking-water. The temporal pattern of lung cancer mortality rate ratios in Region II compared with that in Region V (a low-exposure area) from 1950 to 2000, showed an increase about 10 years after the onset of high arsenic exposure, and peaked in 1986–87, with relative risks of 3.61 (95%CI: 3.13–4.16) and 3.26 (95%CI: 2.50–4.23) for men and women, respectively (Marshall *et al.*, 2007).

(b) Case–control and cohort studies

In northern Chile, a case–control study of 151 cases and 419 controls reported significantly increasing risks with increasing levels of arsenic during the 1958–70 high-exposure period, with an odds ratio increasing to 7.1 (95%CI: 3.4–14.8) (Ferreccio *et al.*, 2000).

In a cohort from south-western Taiwan (China), Chen *et al.* (1986) observed a dose–response relationship between the duration of consumption of artesian well-water containing high levels of arsenic and lung cancer mortality risk, showing the highest age- and gender-adjusted odds ratio among those who consumed artesian well-water for more than 40 years compared with those who never consumed artesian well-water. Another cohort study from south-western Taiwan (China) endemic for arsenic found a smoking-adjusted increased risk for lung cancer in relation to increasing average concentrations of arsenic and increasing cumulative exposure to arsenic (Chiou *et al.*, 1995).

A further study of combined cohorts in south-western (n = 2503) and north-eastern (n = 8088) Taiwan (China) found a synergistic interaction between arsenic in drinking-water and cigarette smoking (Chen *et al.*, 2004).

A case–control study from Bangladesh, conducted in 2003–06, found an elevated risk (odds ratio [OR], 1.65; 95%CI: 1.25–2.18) for male smokers consuming tube well-water with arsenic levels of 101–400 µg/L (Mostafa *et al.*, 2008). In non-smokers, the study did not report an increased risk with increasing arsenic exposure. [The Working Group noted the ecological nature of the exposure estimates, the possibility of greater sensitivity to arsenic exposure among smokers, and the relatively short latent period, with almost two-thirds of the wells put in place in 1990 or later.]

2.3 Cancer of the urinary bladder and of the kidney

The results of the epidemiological studies on arsenic in drinking-water and the risk for cancers of the urinary bladder and of the kidney are summarized in Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.7.pdf.

2.3.1 Ecological studies

In south-western and north-eastern Taiwan (China), the relation between cancer of the urinary bladder and of the kidney and drinking-water containing arsenic was evaluated in many of the studies cited above (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Tsai *et al.*, 1999). Each reported an elevation in mortality from these cancers during various time periods in 1971–94 associated with levels of arsenic in well-water from rural artesian wells, with many reporting a dose–response relationship among both men and women. An additional study, based on incidence records, found comparable risks for bladder cancer (Chiang *et al.*, 1993).

In Region II of Chile, two studies found markedly high SMRs for cancer of the urinary bladder and of the kidney in 1950–92 (Rivara *et al.*, 1997) and in 1989–93 (Smith *et al.*, 1998). In the latter study, mortality from chronic obstructive pulmonary disease was at the expected level, suggesting that smoking was not involved. The temporal pattern of bladder cancer mortality in Region II from 1950–2000 was compared with that in Region V (Marshall *et al.*, 2007). Increased relative risks were reported about 10 years after the start of exposure to high arsenic levels, with peak relative risks of 6.10 (95%CI: 3.97–9.39) for men, and 13.8 (95%CI: 7.74–24.5) for women in the period 1986–94. In Cordoba Province, Argentina, positive trends in SMRs were reported for bladder and kidney cancers associated with estimates of exposure to arsenic in drinking-water (Hopenhayn-Rich *et al.*, 1996, 1998), again with no findings for chronic obstructive pulmonary disease.

[The Working Group noted that kidney cancers consist of both renal cell carcinoma and transitional cell carcinoma of the renal pelvis, the latter often being of the same etiology as bladder cancer. As arsenic causes transitional cell carcinoma of the bladder, merging of the two types of kidney cancer may result in a dilution of the risk estimate for total kidney cancer.]

2.3.2 Case–control and cohort studies

In a case–control study using death certificates (1980–82) from the area in Taiwan (China), endemic for Blackfoot disease, Chen *et al.* (1986) reported increasing trends in odds ratios with increasing duration of consumption of artesian well-water containing arsenic. The highest risks were seen for over 40 years of exposure, with an odds ratio of 4.1 ($P < 0.01$) for bladder cancer in a multivariate analysis, after adjusting for smoking and other factors from next-of-kin interviews.

In case–control studies of incident bladder cancer that included analysis of arsenic species in urine samples, a higher risk associated with arsenic was found among persons with higher MMA^V:DMA^V ratios or, alternatively, with a higher percentage of MMA^V (Chen *et al.*, 2003, 2005a; Steinmaus *et al.*, 2006; Pu *et al.*, 2007a; Huang *et al.*, 2008).

Cohort studies from south-western and north-eastern Taiwan (China) (Chen *et al.*, 1988b; Chiou *et al.*, 1995, 2001; Chen & Chiou, 2001) Japan (Tsuda *et al.*, 1995), and the United Kingdom (Cuzick *et al.*, 1992) each observed elevated bladder cancer risk following long-term exposure to ingested arsenic, with dose–response relationships found where the numbers of cases permitted such an analysis. The study from Taiwan (China), also found an elevated risk of kidney cancer (OR, 2.8; 95%CI: 1.3–5.4, based on nine cases) (Chiou *et al.*, 2001).

2.4 Cancer of the skin

The recognition of arsenic as a carcinogen first came from case series describing skin cancers following the ingestion of medicines containing arsenicals (Hutchinson, 1888; Neubauer, 1947), and exposure to arsenical pesticide residues, and arsenic-contaminated wine (Roth, 1957; Grobe,

1977) or drinking-water, originating from many countries. The characteristic arsenic-associated skin tumours include squamous cell carcinomas arising in keratoses (including Bowen disease), and multiple basal cell carcinomas.

Findings of epidemiological studies on arsenic in drinking-water and risk for skin cancer are summarized in Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.8.pdf.

2.4.1 Ecological studies of prevalence

In south-western Taiwan (China), Tseng *et al.* (1968) found an 8-fold difference in the prevalence of skin cancer lesions from the highest (> 600 µg/L) to the lowest category (< 300 µg/L) of arsenic concentration in artesian wells, after an extensive examination survey of 40421 inhabitants in 37 villages.

2.4.2 Ecological studies based on mortality from cancer of the skin

Studies in Taiwan (China) (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Tsai *et al.*, 1999) analysed skin cancer mortality in relation to levels of arsenic in well-water. These investigations found consistent gradients of increasing risk with average level of arsenic in drinking-water, as measured on the township or precinct level.

Rivara *et al.* (1997) observed an SMR for skin cancer of 3.2 (95%CI: 2.1–4.8), comparing mortality from skin cancer in 1976–92 between Region II and the unexposed control Region VIII of Chile. Later, Smith *et al.* (1998) found SMRs of 7.7 (95%CI: 4.7–11.9) among men and 3.2 (95%CI: 1.3–6.6) among women for the years 1989–93 in Region II of Chile, using national mortality rates as reference. [The Working Group noted that the histological type of skin cancer was reported in only a few instances. Although skin cancer mortality can be influenced by access to health care, the SMRs reported here are so large as to not be explained by any possible confounding.]

2.4.3 Cohort studies

A retrospective cohort study of 789 (437 men, 352 women) of Blackfoot disease patients in Taiwan (China) reported an SMR of 28 (95%CI: 11–59) for skin cancer deaths (based on seven observed deaths), using Taiwan (China) regional rates as reference (Chen *et al.*, 1988b).

In a cohort of 654 persons in south-western Taiwan (China), an observed incidence rate of 14.7 cases of skin cancer/1000 person–years was found (Hsueh *et al.*, 1997), with risks significantly related to duration of living in the area endemic for Blackfoot disease, duration of consumption of artesian well-water, average concentration of arsenic, and index for cumulative exposure to arsenic. Similar findings were observed in a nested case–control study conducted within this cohort (Hsueh *et al.*, 1995).

In Region II of Chile, a decrease in incidence rates of cutaneous lesions (leukoderma, melanoderma, hyperkeratosis, and squamous cell carcinoma) was observed during 1968–71 after a lowering of waterborne arsenic levels from a filter plant, which started operation in 1970 (Zaldívar, 1974).

2.5 Cancer of the liver

2.5.1 Ecological studies

The relation between liver cancer risk and drinking-water contaminated with arsenic was evaluated in many of the studies from south-western Taiwan (China), cited above (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Chiang *et al.*, 1993; Tsai *et al.*, 1999; see Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.9.pdf), with positive associations found in all studies.

In northern Chile, Rivara *et al.* (1997) observed a relative risk for liver cancer mortality of 1.2 (95%CI: 0.99–1.6) in arsenic-exposed Region II compared with Region VIII. Liver cancer mortality in Region II of northern Chile during the period 1989–93 among persons ≥ 30 years of age was not significantly elevated, using national rates as reference (Smith *et al.*, 1998). SMRs were 1.1 (95%CI: 0.8–1.5) both for men and for women. Liaw *et al.* (2008) found an elevated relative risk (10.6; 95%CI: 2.9–39.3, $P < 0.001$) for liver cancer among children in Region II of Chile born in 1950–57 and exposed *in utero* or shortly thereafter, compared to rates in Region V of Chile.

In Cordoba Province, Argentina, SMRs were not related to arsenic exposure (Hopenhayn-Rich *et al.*, 1998).

[The Working Group noted that the finding of an association with liver cancer in Taiwan (China), but not in South America may reflect a more sensitive population in the former region, due to endemic hepatitis B. The elevated risk of those exposed *in utero* and as young children may reflect a combination of greater biological vulnerability in early life (Waalkes *et al.*, 2007) plus the fact that young children consume 5–7 times more water per kilogram body weight per day than adults (NRC, 1993).]

2.5.2 Case–control studies

In a case–control study investigating the consumption artesian well-water containing high concentrations of arsenic and mortality from liver cancer in four townships of south-westernern Taiwan (China), Chen *et al.* (1986) observed an exposure–response relationship between the duration of consumption of the contaminated well-water and risk for liver cancer, adjusted for cigarette smoking, habitual alcohol and tea drinking, and consumption of vegetables and fermented beans.

2.6 Cancer of the prostate

Studies conducted in Taiwan (China) (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Tsai *et al.*, 1999) analysed prostate cancer mortality in relation to levels of arsenic in well-water, with some overlap among the respective study populations. Using several methodological approaches and comparison populations including direct and indirect standardization of rates, all studies reported significant dose–response relationships between the level of arsenic in drinking-water and the risk for prostate cancer mortality (see Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.10.pdf).

In Chile, Rivara *et al.* (1997) found a relative risk of 0.9 (95%CI: 0.54–1.53) for prostate cancer, comparing the 1990 mortality rate for prostate cancer of Region II with that of Region VIII.

2.7 Synthesis

The Working Group reviewed a large body of evidence that covers ecological studies, case–control studies and cohort studies in a variety of settings and populations exposed either by ingestion (primarily to As^{III} and As^{V} in drinking-water) or inhalation (with exposure to a mixture of inorganic arsenic compounds). The evidence also relates to historical exposure from pesticidal and pharmaceutical uses. The epidemiological evidence from drinking-water exposure permits the evaluation of the carcinogenicity that is related to exposure to As^{III} and As^{V}. The epidemiological evidence from inhaled arsenic mixtures permits the evaluation of the carcinogenicity that is related to inorganic arsenic compounds. However, it does not allow a separation of the carcinogenic risk associated with particular arsenic species that occur in these mixtures.

The observed associations between exposure to arsenic in drinking-water and lung cancer, and between exposure to arsenic in air and lung

cancer, cannot be attributed to chance or bias. The evidence is compelling for both the inhalation and ingestion routes of exposure. There is evidence of dose–response relationships within exposed populations with both types of exposure.

The observed association between exposure to arsenic in drinking-water and bladder cancer cannot be attributed to chance or bias. There is evidence of dose–response relationships within exposed populations.

The observed association between exposure to arsenic in drinking-water and skin cancer cannot be attributed to chance or bias. There is evidence of dose–response relationships within exposed populations. The evidence is primarily for squamous cell carcinoma of the skin.

Although the data for kidney cancer are suggestive of a relationship with exposure to arsenic in drinking-water, overall, the small possibility of chance or bias cannot be completely ruled out.

The evidence for an association between liver cancer and long-term exposure to arsenic in drinking-water relies on mortality data. Although the data strongly suggest a causal association with some evidence of a dose–response relationship, the Working Group could not rule out possible chance or bias. The evidence comes mainly from Taiwan (China) where hepatitis B is highly prevalent.

The evidence for an association for prostate cancer and long-term exposure to arsenic in drinking-water relies on mortality data. In the studies from Taiwan (China), there is some evidence of a dose–response relationship. However, the data from South America are not consistent with this observation. Although the evidence on prostate cancer suggests the possibility of a causal association, the Working Group could not rule out the possibility of chance or bias.

3. Cancer in Experimental Animals

Over the years, it has proved difficult to provide evidence for the carcinogenesis of inorganic arsenic compounds. More recent work has focused on methylated arsenic metabolites in humans or exposure to inorganic arsenic during early life, and has provided the information to show potential links between arsenic and carcinogenesis.

Studies published since the previous *IARC Monograph* (IARC, 2004) are summarized below.

3.1 Oral administration

3.1.1 Mouse

The oral administration of sodium arsenate in drinking-water for 18 months increased lung tumour multiplicity and lung tumour size in male strain A/J mice (Cui *et al.*, 2006; see Table 3.1).

Similarly, drinking-water exposure to the organo-arsenical DMA^V for 50 weeks or more increased the incidence and multiplicity of lung adenoma or carcinoma in strain A/J mice (Hayashi *et al.*, 1998), and increased lung tumours in mutant *Ogg*–/– mice (which cannot repair certain types of oxidative DNA damage) but not in *Ogg*+/+ mice (Kinoshita *et al.*, 2007; see Table 3.2).

3.1.2 Rat

In male F344 rats, the oral administration of DMA^V in drinking-water for up to 2 years produced clear dose–response relationships for the induction of urinary bladder transitional cell carcinoma and combined papilloma or carcinoma (Wei *et al.*, 1999, 2002).

When DMA^V was added to the feed of male and female F344 rats for 2 years, a clear dose–response relationship for urinary bladder benign and/or malignant transitional cell tumours

Table 3.1 Studies of cancer in experimental animals exposed to sodium arsenate (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, A/J (M) 18 mo Cui *et al.* (2006)	0, 1, 10, 100 ppm arsenate in drinking-water, *ad libitum* 30/group	Lung (adenomas): 0/19, 0/13, 0/15, 4/30 (13%)	[NS, (any dose)][a]	Age at start, 5 wk Purity, NR Redundant Student *t*-test used for multiple comparisons of lung tumour multiplicity and size Survival significantly increased at high dose Non-dose-related, modest changes in bw, lung weight, and lung bw ratio
		Lung (adenocarcinomas): 9/19 (47%), 10/13 (77%), 11/15 (73%), 19/30 (63%)	[NS, (any dose)][a]	
		Average tumours/mouse lung: 0.59, 1.1, 1.3, 1.4[b]	$P < 0.01$ (all doses)	
		Average number tumours > 4 mm/mouse lung: 17, 32, 44, 60[b]	$P < 0.01$ (all doses)	

[a] Performed during review. One-sided Fisher Exact test–control versus all treated.
[b] Numbers are estimates at review because data are presented graphically in original work.
bw, body weight; M, male; mo, month or months; NR, not reported; NS, not significant; wk, week or weeks

occurred in female but not male rats (Arnold *et al.*, 2006). Preneoplasia (urothelial cell hyperplasia) was clearly increased in female rats (Arnold *et al.*, 2006; see Table 3.2).

In male F344 rats, the oral administration of trimethylarsine oxide in drinking-water for 2 years caused a significant increase of benign liver tumours (adenoma) (Shen *et al.*, 2007; see Table 3.3).

Oral exposure to MMA^V for 2 years was negative in a comprehensive dose–response study including male and female rats and mice, although body weight suppression and reduced survival with the higher doses confounded the rat segment of the study (Arnold *et al.*, 2003; see Table 3.4).

A 2-year dose–response study with sodium arsenite showed some evidence of renal tumour formation in female Sprague-Dawley rats but not in males (Soffritti *et al.*, 2006). Tumour incidence did not reach significance (see Table 3.5).

3.2 Intratracheal administration

3.2.1 Hamster

Repeated weekly intratracheal instillations of calcium arsenate, at levels sufficient to caused moderate early mortality, increased lung adenoma formation in male Syrian golden hamsters when observed over their lifespan (Pershagen & Björklund, 1985).

In a similarly designed study, male hamsters received multiple weekly intratracheal instillations of calcium arsenate at the start of the experiment, and developed an increased incidence of lung adenoma formation, and combined lung adenoma or carcinoma formation over their lifespan (Yamamoto *et al.*, 1987; see Table 3.6).

Intratracheal instillations of calcium arsenite increased the incidence of respiratory tract carcinoma and combined adenoma, papilloma and adenomatoid lesion formation in male Syrian Hamsters (Pershagen *et al.*, 1984; see Table 3.7).

Table 3.2 Studies of cancer in experimental animals exposed to dimethylarsinic acid, DMA^V (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, A/J (M) 50 wk Hayashi *et al.* (1998)	0, 50, 200, 400 ppm DMA^V in drinking-water, *ad libitum* 24/group	Number of mice with lung papillary adenomas or adenocarcinomas: 2/14 (14%), 5/14 (36%), 7/14 (50%), 10/13 (77%)	$P < 0.01$ (high dose)	Age at start, 5 wk Purity, NR Survival unremarkable [Only histologically confirmed tumours were considered by the Working Group]
Mouse, *Ogg1*-/- and *Ogg1*+/+ (M, F) 72 wk Kinoshita *et al.* (2007)	0, 200 ppm DMA^V in drinking-water, *ad libitum*; controls received tap water 10/group (*Ogg1*-/-) 12/group (*Ogg1*+/+)	***Ogg1*-/-:** Tumour-bearing mice (any site): 0/10, 10/10 (100%) *Lung lesions–* Hyperplasias: 10/10 (100%), 10/10 (100%) Adenomas: 0/10, 2/10 (20%) Adenocarcinomas: 0/10, 3/10 (30%) Total lung tumours: 0/10, 5/10 (50%) Tumours/mouse: 0, 0.5 ***Ogg1*+/+:** Tumour-bearing mice (any site): 5/10 (50%), 6/10 (60%) *Lung lesions–* Hyperplasias: 2/10 (20%), 10/10 (100%) Adenomas: 1/10 (10%), 0/10 Adenocarcinomas: 0/10, 0/10 Total tumours: 1/10 (10%), 0/10 Tumours/mouse: 0.1, 0 Tumours/mouse: 0.1, 0	$P < 0.01$ NS $P < 0.05$ $P < 0.05$ [$P < 0.01$[b]] NS NS NS NS NS	Age at start, 14 wk Purity, 99% Bw and food and water consumption unremarkable Left lobe and visible lung nodules used for histopathological tumour analysis Treated *Ogg1*–/– showed modest decreased survival (~20%) late compared to phenotypic control Small groups

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M) 104 wk Wei *et al.* (1999)[d], 2002)	0, 12.5, 50, 200 ppm DMA^V in drinking-water, *ad libitum* 36/group	Urinary bladder (hyperplasias): 0/28, 0/33, 12/31 (39%), 14/31 (45%) Urinary bladder (papillomas): 0/28, 0/33, 2/31 (2%), 2/31 (2%) Urinary bladder (carcinomas): 0/28, 0/33, 6/31 (19%), 12/31 (39%) Urinary bladder (papillomas or carcinomas): 0/28, 0/33, 8/31 (26%), 12/31 (39%)	$P < 0.01$ (middle and high dose) NS $P < 0.05$ (middle dose) $P < 0.01$ (high dose) $P < 0.01$ (middle and high dose)	Age at start, 10 wk Purity, 99% Survival and food intake unaltered Transient bw suppression early with high and middle dose but then similar to control Water intake increased at highest two doses Incidence rates based on rats at risk (surviving to time of the first bladder tumour at 97 wk) Extensive necropsy
Rat, F344 (M, F) 104 wk Arnold *et al.* (2006)	0, 2, 10, 40, 100 ppm DMA^V in feed, *ad libitum* 60/group	**Females** Urothelial cell (hyperplasias, simple, nodular and papillary): 0/60, 1/59 (2%), 0/60, 29/59 (49%), 48/60 (80%) Urinary bladder (papillomas): 0/60, 0/59, 0/60, 0/59, 4/60 (7%) Urinary bladder (carcinomas): 0/60, 0/59, 0/60, 0/59, 6/60 (10%) Urinary bladder (papillomas and carcinomas combined): 0/60, 0/59, 0/60, 0/59, 10/60 (3%) **Males** Urothelial cell (hyperplasias, simple, nodular and papillary): 0/60, 0/59, 0/60, 6/58 (10%), 40/59 (68%) Urinary bladder (papillomas): 0/60, 0/59, 1/60 (2%), 1/58 (2%), 0/59 Urinary bladder (carcinomas): 0/60, 1/59 (2%), 0/60, 0/58, 2/59 (3%) Urinary bladder (papillomas and carcinomas combined): 0/60, 1/59 (2%), 1/60 (2%), 1/58 (2%), 2/59 (3%)	$P < 0.01$ (trend) [$P < 0.01$ (highest, and second highest dose)][b] [NS (high dose)][b] $P < 0.01$ (trend)[c] [$P < 0.05$ (high dose)][b] $P < 0.01$ (trend)[c] [$P < 0.05$ (high dose)][b] $P < 0.01$ (trend) [$P < 0.01$ (high dose)][b] [NS (high dose)][b] $P < 0.01$ (trend)[c] [NS (high dose)][b] $P < 0.01$ (trend)[c] [NS (high dose)][b]	Purity > 99%; age, 5 wk Complete necropsies performed No treatment-related differences in mortality or bw Sporadic changes in food consumption not treatment-related Water consumption increased with treatment Water consumption increased with treatment

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F1 (F) 104 wk Arnold *et al.* (2006)	0, 8, 40, 200, 500 ppm DMA^V in feed, *ad libitum* 56/group	**Females** No treatment-related changes in urinary bladder preneoplasia or tumour incidence noted Any organ (fibrosarcomas): 3/56 (5%), 0/55, 1/56 (2%), 1/56 (2%), 6/56 (11%) **Males** No treatment-related changes in urinary bladder preneoplasia or tumour incidence noted	$P < 0.01$ (high dose)	Age at start, 5 wk Purity 99% Complete necropsies performed Survival, bw and water consumption unchanged Sporadic, small changes in food consumption early Fibrosarcomas not considered related to treatment by authors Bw reduced at 500 ppm throughout study

[a] Data also included descriptive statistics (i.e. SD).
[b] Performed during review. One-sided Fisher exact test control versus treated.
[c] Trend analysis performed after combination of female and male data for urinary bladder lesions from this same study (Arnold *et al.*, 2006).
[d] Short communication of tumour data only.
[e] On a C57BL/6 background.
[f] As stated by the authors.
[g] The lack of information on group size and the lack of descriptive statistics makes these data impossible to independently re-evaluate for statistical significance.
bw, body weight; F, female; M, male; NR, not reported; NS, not significant; wk, week or weeks

Table 3.3 Studies of cancer in experimental animals exposed to trimethylarsine oxide (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M) 2 yr Shen *et al.* (2003)	0, 50, 200 ppm trimethylarsine oxide in drinking-water, *ad libitum* 42–45; 42 controls	Liver (adenomas): 6/42 (9%), 10/42 (14%), 16/45 (24%)	$P < 0.05$ (high dose)	Age at start, 10 wk Purity, 99% Body weights, food intake, water intake, survival rate, and average survival unaltered with treatment Extensive necropsy performed Various other sites negative

bw, body weight; M, male; yr, year or years

3.3 Intravenous administration

3.3.1 Mouse

Multiple intravenous injections of sodium arsenate in male and female Swiss mice provided no evidence of elevated tumour formation (Waalkes *et al.*, 2000; see Table 3.8).

3.4 Transplacental and perinatal exposures

3.4.1 Mouse

Pregnant mice were treated subcutaneously with arsenic trioxide on a single specific day during gestation (Days 14, 15, 16 or 17), and the offspring were then treated subcutaneously on *postpartum* Days 1, 2 and 3 with arsenic trioxide. The offspring initially treated on Day 15 of gestation developed an excess of lung adenoma compared to controls, and the other groups did not (Rudnai & Borzsanyi, 1980, 1981; see Table 3.9).

Pregnant C3H mice were exposed to various doses of sodium arsenite in the drinking-water from Days 8–18 of gestation. They were allowed to give birth and their offspring were put into gender-based groups at weaning. Over the next 90 weeks, arsenic-treated female offspring developed dose-related benign and/or malignant ovarian tumours, and lung adenocarcinoma. During the next 74 weeks, a dose-related increase in the incidences of liver adenoma and/or carcinoma, and adrenal cortical adenoma was observed in the male offspring (Waalkes *et al.*, 2003).

A second study looked at the carcinogenic effects in C3H mice of various doses of sodium arsenite (two levels) in the maternal drinking-water from Days 8 to 18 of gestation, with or without subsequent 12-*O*-tetradecanoyl phorbol-13-acetate (TPA) applied to the skin of the offspring after weaning from 4–25 weeks of age. Over the next 2 years, with arsenic alone, the female offspring developed an increased incidence of ovarian tumours. The male offspring developed arsenic dose-related increases in the incidences of liver adenoma and/or carcinoma and adrenal cortical adenoma (Waalkes *et al.*, 2004).

Pregnant CD1 mice received sodium arsenite (one level) in the drinking-water from gestation Days 8 to 18, were allowed to give birth, and the female (Waalkes *et al.*, 2006a) or male (Waalkes *et al.*, 2006b) offspring were treated with diethylstilbestrol or tamoxifen subcutaneously on *postpartum* Days 1, 2, 3, 4 and 5. In female offspring over the next 90 weeks, arsenic exposure alone

Table 3.4 Studies of cancer in experimental animals exposed to monomethylarsonic acid, MMA^V (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F1 (M, F) 104 wk Arnold *et al.* (2003)	0, 10, 50, 200, 400 ppm MMA^V in feed, *ad libitum* 52/group/sex	No treatment-related changes		Age at start, 6 wk Purity, 99% Bw reduced at 400 ppm throughout study Food and water consumption similar or increased at the two higher doses Survival unremarkable Complete necropsy performed
Rat, F344 (M, F) 104 wk Arnold *et al.* (2003)	0, 50, 400, 1 300[a] ppm MMA^V in feed, *ad libitum* 60/group/sex	No treatment-related changes		Age at start, 6 wk Purity, 99% Bw reduced at two highest doses in second half of study Food consumption generally similar Water consumption similar or increased at the two higher doses Survival reduced at high dose Complete necropsy performed

[a] Due to a high mortality in male and female rats fed this level, it was reduced to 1000 ppm during Week 53, and further reduced to 800 ppm during Week 60.
bw, body weight; F, female; M, male; wk, week or weeks

Table 3.5 Studies of cancer in experimental animals exposed to sodium arsenite (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (M, F) 167 wk (lifespan) Soffritti *et al.* (2006)	0, 50, 100, 200 mg/L $NaAsO_2$ in drinking-water, *ad libitum* from onset to 104 wk 50/group	Kidney (tumours): F– 1/50 (2%), 1/50 (2%), 5/50 (10%), 5/50 (10%)[c] M– 0/50, 2/50 (4%), 2/50 (4%), 0/50	NS for both sexes	Age at start, 8 wk Purity 98% Complete necropsy performed Reduced water and food intake especially at two highest doses Dose-related reduced bw

[a] As stated by the authors.
[b] The lack of information on group size and lack of descriptive statistics makes the data from this work impossible to re-evaluate for statistical significance.
[c] Includes three carcinomas at the high dose and one at the second highest dose in females and a carcinoma in females at the second highest dose.
Bw, body weight; F, female; M, male; NS, not significant; wk, week or weeks

increased the incidence of tumours of the ovary, uterus, and adrenal cortex. In the male offspring, prenatal arsenic exposure alone increased liver adenoma and/or carcinoma, lung adenocarcinoma, and adrenal cortical adenoma (see Table 3.10).

3.5 Studies in which arsenic modifies the effects of other agents

3.5.1 Mouse

Mice exposed to DMA^V in drinking-water after subcutaneous injection of 4-nitroquinoline 1-oxide showed an increase in lung tumour multiplicity compared to mice exposed to the organic carcinogen alone (Yamanaka *et al.*, 1996). In K6/ODC mice first treated topically with 7,12-dimethylbenz[α]anthracene (DMBA) then with DMA^V in a cream applied to the same skin area for 18 weeks, the organo-arsenical doubled the skin tumour multiplicity compared to treatment with DMBA alone (Morikawa *et al.*, 2000; see Table 3.11). [The Working Group noted that this study had too few DMA^V controls for an appropriate interpretation.]

In the studies of Germolec *et al.* (1997, 1998), oral sodium arsenite was given to Tg.AC mice with TPA by skin painting, and an approximately 4-fold increase in skin tumour response was reported.

Combined treatment with oral sodium arsenite in drinking-water and multiple exposures to excess topical UV irradiation in Crl:SKH-*hr*BR hairless mice showed that arsenic treatment alone was consistently without carcinogenic effect, but markedly enhanced UV-induced skin tumours including squamous cell carcinoma (Rossman *et al.*, 2001; Burns *et al.*, 2004; Uddin *et al.*, 2005). In another skin study, mice exposed to topical 9,10-dimethyl-1,2-benzanthracene for 2 weeks concurrently with oral sodium arsenate in drinking-water for 25 weeks showed that arsenic treatment alone was without carcinogenic effect, but enhanced skin tumour multiplicity and tumour size when combined with the organic carcinogen compared to the organic carcinogen alone (Motiwale *et al.*, 2005; see Table 3.12).

When pregnant Tg.AC mice were treated with oral sodium arsenite in drinking-water from Days 8–18 of gestation, and their offspring were topically exposed to TPA from 4–40 weeks

Table 3.6 Studies of cancer in experimental animals exposed to calcium arsenate (intratracheal instillation)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Hamster, Syrian golden (M) ~145 wk (lifespan) Pershagen & Björklund (1985)	0, ~3 mg As/kg bw in 0.15 mL saline once/wk for 15 wk 41; 29 controls	Lung (adenomas): 0/26, 4/35 (11%)	$P < 0.05$	Age at start, 8 wk Purity, ultrapure Mortality during dosing ~15%; mortality increased in arsenate group during second yr Dose approximate
Hamster, Syrian golden (M) Up to 115 wk in treated animals, and 121 wk in controls (lifespan) Yamamoto *et al.* (1987)	0, 0.25 mg As in 0.1 mL saline once/wk for 15 wk 30; 22 controls	Lung (adenomas): 0/22, 6/25 (24%) Lung (carcinomas): 1/22 (4%), 1/25 (4%) Lung (adenomas and carcinomas combined): 1/22 (4%), 7/25 (3%)	[$P < 0.01$[a]] NS *P*-value not reported but stated as significant [$P < 0.01$[a]]	Age at start, 8 wk Purity, chemical grade Instillations caused 10% mortality and reduced survival ~10% post-instillation Bw not recorded during experiment

[a] Calculated by the Working Group. One-sided Fisher exact test control versus treated.
bw, body weight; M, male; NS, not significant; wk, week or weeks

Table 3.7 Studies of cancer in experimental animals exposed to arsenic trioxide (intratracheal instillation)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Hamster, Syrian golden (M) Up to ~140 wk (lifespan) Pershagen *et al.* (1984)[a]	0 or ~3 mg As/kg bw in 0.15 mL saline once/wk for 15 wk 67; 68 controls	Larynx, trachea, bronchus, or lung (carcinomas): 0/53, 3/47 (6%) Larynx, trachea, bronchus, or lung (adenomas, adenomatoid lesions, and papillomas combined): 7/53 (13%), 24/47 (51%)	NS [$P < 0.01$]	Age at start, 7–9 wk Purity, 99.5% Doses approximate Instillation mixture for arsenic contained carbon dust and 2 mM sulfuric acid (not in controls) Significant mortality during dosing (29%) "Adenomatoid lesion" not defined, presumably focal hyperplasia

[a] Arsenic trioxide was also given with benzo[*a*]pyrene and the combination appeared to increase combined adenoma, adenocarcinoma and adenosquamous carcinoma in the bronchi and lungs compared to benzo[*a*]pyrene alone but the data are listed (total tumours/group and not incidence) such that this cannot be independently confirmed.

bw, body weight; M, male; NS, not significant; wk, week or weeks

Table 3.8 Studies of cancer in experimental animals exposed to sodium arsenate (intravenous exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Swiss CR:NIH(S) (M, F) 96 wk Waalkes *et al.* (2000)	0, 0.5 mg As/kg bw in 10 mL/kg in saline once/wk for 20 wk staring at onset; controls received saline[a] 25/group/sex	M Lymphomas: 1/25 (4%), 1/25 (4%)	NS	Age at start, 8 wk Purity, NR Survival and bw not remarkable No leukaemias were observed
		Testicular interstitial cell hyperplasias: 8/25 (32%), 16/25 (64%)	$P < 0.05$	
		Skin hyperkeratosis: 1/25 (4%), 5/25 (20%)	NS	
		F Lymphomas: 5/25 (20%), 3/25 (12%)	NS	
		Uterine cystic hyperplasias: 5/25 (20%), 14/25 (56%)[b]	$P < 0.05$	

[a] Based on the treatment regimen of Osswald & Goerttler (1971).

[b] A uterine adenocarcinoma was also observed with arsenate treatment that is noteworthy because of its spontaneous rarity in historical controls of this strain.

bw, body weight; F, female; M, male; NR, not reported; NS, not significant; wk, week or weeks

Table 3.9 Studies of cancer in experimental animals exposed to arsenic trioxide (perinatal exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, CFLP (NR) 1 yr Rudnai & Borzsanyi (1980), Rudnai & Borzsanyi (1981)[a]	Single dose of 1.2 mg/kg arsenic trioxide bw s.c. at gestation Day 14, 15, 16, or 17 Test offspring: 5 µg arsenic trioxide/mouse s.c. postpartum Day 1, 2 and 3 Controls untreated Offspring group sizes at start (NR)	Lung (adenomas and adenocarcinomas):[b] Control–3/17 (17%) Day 14–14/36 (39%) Day 15–12/19 (63%) Day 16–3/20 (15%) Day 17–6/20 (30%)	$P < 0.01$ (Day 15)[b]	Purity stated as "purum" Pregnancy verified by smear and when positive designated Day 0 Dam number used to derive offspring groups NR Lung and gross lesions histologically examined Survival and bw NR Gender NR and probably mixed Numbers of specific lung tumours NR

[a] In Hungarian. Tumour incidence data are numerically the same for this and the Rudnai & Borzsanyi (1980) manuscript, but vary in that the treatment day of pregnancy which lead to a significant increase in lung adenoma in the first paper (Day 15) shifted to one day later in the second paper (Day 16). Communication with the primary author revealed that this discrepancy in the re-reporting (Rudnai & Borzsanyi, 1981) is due to a difference in calling the first day on which pregnancy was indicated Day 1 of gestation rather than Day 0 as in the original report (Rudnai & Borzsanyi, 1980). Thus, the treatment regimen and data from the primary paper are herein reported.

[b] The gestational treatment day is given in parentheses before incidence or after indication of significance.

bw, body weight; NR, not reported; s.c., subcutaneously; yr, year or years

Table 3.10 Studies of cancer in experimental animals exposed to sodium arsenite (transplacental exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, C3H/HeNCr (M, F) 90 wk (*postpartum*) for F 74 wk (*postpartum*) for M Waalkes *et al.* (2003)	Maternal exposure: 0, 42.5, 85 ppm As in drinking-water, *ad libitum* from gestation Day 8–18 Offspring; 25/group/sex	**Females** Ovary (tumours): Benign–2/25 (8%), 4/23 (17%), 8/24 (33%)	$P < 0.05$ (high dose plus trend)	Purity,[a] NR 10 Pregnant mice used to derive each group of offspring Offspring weaned at 4 wk Maternal water consumption and bw unaltered Offspring bw unaltered Survival in offspring unaltered in females Survival reduced at high dose in due to liver carcinoma in males
		Malignant–0/25, 2/23 (9%), 1/24 (4%)	NS	
		Benign or malignant combined–2/25 (8%), 6/23 (26%), 9/24 (37%)	$P < 0.05$ (high dose) $P < 0.05$ (trend)	
		Lung (carcinomas): 0/25, 1/23 (4%), 5/24 (20%)	$P < 0.05$ (high dose) $P < 0.05$ (trend)	
		Males Liver (adenomas): 9/24 (37%), 9/21 (43%), 20/23 (87%)	$P < 0.01$ (high dose)	
		Liver (hepatocellular carcinomas): 2/24 (8%), 8/21 (38%), 14/23 (61%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Liver (adenomas or hepatocellular carcinomas): 10/24 (42%), 11/21 (52%), 20/23 (87%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Liver tumours/mouse: 0.87, 1.81, 4.91	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Adrenal cortex (adenomas): 9/24 (37%), 14/21 (67%), 21/23 (91%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Adrenal adenomas/mouse: 0.71, 1.10, 1.57	$P < 0.05$ (high dose) $P < 0.05$ (trend)	

Table 3.10 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, C3H/HeNCr (M, F) 104 wk (*postpartum*) Waalkes *et al.* (2004)	Maternal exposure: 0, 42.5, 85 ppm As in drinking-water, *ad libitum* from gestation Day 8–18 Offspring exposure: topical 2 µg[b] TPA/0.1 mL acetone, twice/wk from 4–25 wk of age applied to shaved back, controls received acetone Offspring groups: 25/group/sex	**Females** Liver (adenomas or hepatocellular carcinomas): Without TPA–3/24 (12%), 6/23 (26%), 4/21 (19%) With TPA–3/24 (12%), 6/22 (27%), 8/21 (38%) Liver tumour multiplicity (tumours/mouse): Without TPA–0.13, 0.41, 0.29 With TPA–0.13, 0.32, 0.71 Ovary (tumours):[c] Without TPA–0/24, 5/23 (22%), 4/21 (19%) With TPA–0/24, 5/22 (23%), 4/21 (19%) Lung (adenomas): Without TPA–1/24 (4%), 2/23 (9%), 2/21 (9%) With TPA–1/24 (4%), 2/22 (9%), 6/21 (29%) **Males** Liver (tumours): Adenomas without TPA–10/24 (42%), 12/23 (52%), 19/21 (90%) Adenomas with TPA–8/23 (35%), 12/23 (52%), 16/21 (76%) Hepatocellular carcinomas without TPA–3/24 (12%), 8/23 (35%), 10/21 (48%) Hepatocellular carcinomas with TPA–2/23 (9%), 6/23 (26%), 7/21 (33%) Adenomas or hepatocellular carcinomas without TPA–12/24 (50%), 14/23 (52%), 19/21 (90%)	 NS $P < 0.05$ (high dose and trend) NS $P < 0.05$ (high dose and trend) $P < 0.05$ (both doses) $P < 0.05$ (both doses) NS $P < 0.05$ (high dose and trend) $P < 0.05$ (high dose) $P < 0.01$ (trend) $P < 0.05$ (high dose) $P < 0.01$ (trend) $P < 0.05$ (high dose) $P < 0.01$ (trend) $P < 0.05$ (high dose and trend) $P < 0.05$ (high dose) $P < 0.01$ (trend)	Purity,[a] NR 10 Pregnant mice used to derive each group of offspring Litters culled at 4 d *postpartum* to no more than 8 pups Maternal water consumption and bw unaltered Small bw reductions (~10%) occurred late (> 95 wk) in the high-dose (85 ppm) female offspring TPA did not alter bw Survival unaltered Inclusion of TPA did not have an impact on skin cancers Arsenic group not given TPA due to liver carcinoma (males)

Table 3.10 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Waalkes *et al.* (2004) (contd.)		Adenomas or hepatocellular carcinomas with TPA–9/23 (39%), 15/23 (65%), 18/21 (90%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Multiplicity without TPA: 0.75, 1.87, 2.14	$P < 0.05$ (both doses) $P < 0.01$ (trend)	
		Multiplicity with TPA: 0.61, 1.44, 2.14	$P < 0.05$ (both doses) $P < 0.01$ (trend)	
		Adrenal cortex (adenomas): Without TPA–9/24 (37%), 15/23 (65%), 15/21 (71%) With TPA–7/23 (30%), 15/23 (65%), 12/21 (57%)	$P < 0.05$ (high dose and trend) $P < 0.05$ (low dose)	
		Lung (adenomas): Without TPA–4/24 (17%), 6/23 (26%), 5/21 (24%) With TPA–2/23 (9%), 10/23 (43%), 5/21 (24%)	NS $P < 0.05$ (low dose)	
Mouse, CD1 (M, F) 90 wk (*postpartum*) Waalkes *et al.* (2006a, b)[k]	Maternal exposure: 0, 85 ppm As in drinking-water, *ad libitum* from gestation Day 8–18 Offspring exposure: *Postpartum* Day 1, 2, 3, 4, and 5 2 µg DES[d]/pup/d s.c., or 10 µg TAM[e]/pup/d s.c., or vehicle (corn oil; control) (control, As, DES, TAM, As + DES, As + TAM) 35/group/sex	**Females** Ovary (tumours):[h] 0/33, 7/34 (21%), 2/33 (6%), 1/35 (3%), 9/33 (26%), 5/35 (14%)	$P < 0.05$ (As, As + DES, As + TAM)	Purity 97.0% $NaAsO_2$ 12 Pregnant mice used to derive each group of offspring Litters culled after birth to no more than 8 pups Maternal water consumption unaltered Maternal and offspring bw unaltered
		Uterus (adenomas): 0/33, 3/34 (9%), 0/33, 0/35, 0/33, 0/35	NS	
		Uterus (carcinomas): 0/33, 2/34 (6%), 0/33, 2/35 (6%), 7/33 (21%), 2/35 (6%)	$P < 0.05$ (As + DES)	
		Uterus (adenomas or carcinomas): 0/33, 5/34 (15%), 0/33, 2/35 (6%), 7/33 (21%), 2/35 (6%)	$P < 0.05$ (As, As + DES)	
		Vagina (carcinomas): 0/33, 0/34, 1/33, 0/35, 5/33[g] (15%), 0/35	$P < 0.05$ (As + DES)	
		Adrenal cortex (adenomas): 1/33 (3%), 9/34 (26%), 3/33 (9%), 2/35 (6%), 8/33 (24%), 7/35 (20%)	$P < 0.05$ (As, As + DES, As + TAM)	
		Urinary bladder lesions:		

Table 3.10 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Waalkes *et al.* (2006a, b) (contd.)		Hyperplasias– 1/33 (3%), 5/34 (15%), 1/33 (3%), 0/35, 10/33 (30%), 9/35 (26%)	$P < 0.05$ (As + DES, As + TAM)	
		Papillomas– 0/33, 0/34, 0/33, 0/35, 0/33, 1/35 (3%)	NS	
		Carcinomas[i]– 0/33, 0/34, 0/33, 0/35, 3/33 (9%), 0/35	NS	
		Total proliferative lesions[j]– 1/33 (3%), 5/34 (15%), 1/33 (3%), 0/35, 13/33[g] (38%), 10/35[g] (29%)	$P < 0.05$ (As + DES, As + TAM)	
		Liver (tumours any type): 0/33, 4/34 (12%), 1/33 (3%), 0/35, 5/33 (15%), 4/35 (11%)	$P < 0.05$ (As + DES)	
		Males Liver (tumours):		Purity sodium arsenite 97.0%; DES 99%, TAM 99%
		Adenomas– 2/35 (6%), 8/35 (23%), 1/33 (3%), 0/30, 12/29 (41%), 9/30 (30%)	$P < 0.05$ (As, As + DES, As + TAM)	Bw transiently reduced (~15%) by DES or TAM early but recovery to control levels by 5–20 wk *postpartum* Survival unaltered by prenatal arsenic alone. Survival reduced in all other treatment groups (DES, TAM, As + DES, As + TAM) from ~20 wk on compared to control[l] (males)
		Hepatocellular carcinomas– 0/35, 5/35 (14%), 0/33, 0/30, 4/29 (14%), 5/30 (17%)	$P < 0.05$ (As, As + DES, As + TAM)	
		Adenomas or carcinomas– 2/35 (6%), 11/35 (31%), 1/33 (3%), 0/30, 14/29 (48%), 14/30 (47%)	$P < 0.05$ (As, As + DES,)	
		Lung (adenocarcinomas): 2/35 (6%), 9/35 (26%), 2/33 (6%), 0/30, 4/29 (14%), 6/30 (20%)	$P < 0.05$ (As)	
		Adrenal cortex (adenomas): 0/35, 13/35 (37%), 0/33, 0/30, 9/29 (31%), 11/30 (37%)	$P < 0.05$ (As, As + DES, As + TAM)	
		Urinary bladder lesions: Hyperplasias– 0/35, 3/35 (9%), 4/33 (12%), 3/30 (10%), 13/29[g] (45%), 9/30[g] (30%)	$P < 0.05$ (As + DES, As + TAM)	
		Papillomas– 0/35, 0/35, 0/33, 0/30, 0/29, 3/30 (10%)	NS	

Table 3.10 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Waalkes *et al.* (2006a, b) (contd.)		Carcinomas[i]– 0/35, 0/35, 0/33, 0/30, 1/29 (3%), 1/30 (3%)	NS	
		Papillomas or carcinomas– 0/35, 0/35, 0/33, 0/30, 1/29 (3%), 4/30[g] (13%)	$P < 0.05$ (As + TAM)	
		Total proliferative lesions[j]– 0/35, 3/35 (9%), 4/33 (12%), 3/30 (10%), 13/29[g] (45%), 14/30[g] (40%)	$P < 0.05$ (As + DES, As + TAM)	

[a] Purity given in Waalkes *et al.* (2006a) using same chemical source is 97.0%.
[b] 12-*O*-tetradecanoyl phorbol-13-acetate.
[c] Exclusively epithelial and primarily adenoma.
[d] Diethylstilbestrol
[e] Tamoxifen
[f] Included benign and malignant epithelial and mesenchymal tumours within components of the urogenital system (ovary, oviduct, uterus, cervix, vagina, kidney, and urinary bladder).
[g] Incidence for arsenic plus DES or arsenic plus TAM was significantly ($P < 0.05$) higher than arsenic alone.
[h] Primarily adenoma.
[i] Exclusively transitional cell carcinoma.
[j] Defined by the authors as the incidence of mice bearing at least one uroepithelial preneoplasia (hyperplasia), papilloma, or carcinoma.
[k] Run concurrently with and derived from the same mothers as the females in Waalkes *et al.* (2006a) study but reported separately.
[l] Reduced survival in these groups appeared dependent on moderate to extensive kidney damage due to DES and TAM in male mice and appeared unrelated to arsenic exposure.
[m] Two renal tumours also occurred in this group including, an adenoma and a renal cell carcinoma, against none in control, which are noteworthy because of their rare spontaneous occurrence in mice.
d, day or days; DES, diethylstilbestrol; F, female; M, male; NR, not reported; NS, not significant, s.c., subcutaneously; TAM, tamoxifen; wk, week or weeks

Table 3.11 Studies where arsenicals given after other agents enhance carcinogenesis while having no effect alone in experimental animals

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, ddy (M) 25 wk Yamanaka *et al.* (1996)	Initiation 10 mg 4NQO[e]/kg bw s.c. then 200 or 400 ppm DMA^V in drinking-water for 25 wk Groups: 4NQO alone, 4NQO + 200 ppm DMA, 4NQO + 400 ppm DMA 9–13/group	Macroscopic lung tumours/mouse: 0.22, 3.92, 4.38	$P < 0.05$ (high dose)	Age at start, 6 wk DMA^V purity, NR Bw and survival unremarkable DMA^V alone group not included Lung only Microscopic analysis of lung tumours not reported (largely confirmed as tumours) Small group sizes
Mouse, *K6/ODC* (C57BL/6J background) 20 wk Morikawa *et al.* (2000)	Single 50 µg dose of DMBA[f]/mouse topical dorsal skin at Week 1; then 3.6 mg DMA^V/mouse in "neutral cream" to dorsal skin twice/wk, Week 2–19 Groups: DMBA, DMBA + DMA^V 7; 8 controls (DMBA)	Macroscopic skin tumours/mouse: 9.7, 19.4	$P < 0.05$	Age at start, 10–14 wk DMA^V purity, NR Bw and survival unremarkable DMA^V-alone group had only 2 mice; skin tumours not reported Small group sizes Skin only No quantitative microscopic analysis of skin tumours
Rat, Wistar (M) 175 d Shirachi *et al.* (1983)	Sodium arsenite Partial heptectomy, 18–24 h later 30 mg DEN[a]/kg i.p.; 7 d later 160 ppm As in drinking-water Number at start, NR	Renal tumours: 0/10, 1/7 (14%), 0/9, 7/10 (70%)	$P < 0.05$	Age at start, NR Purity, NR Arsenic lowered bw and water intake Limited reporting and never reported in full

Table 3.11 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344/DuCrj (M) 30 wk Yamamoto *et al.* (1995)	Initial pretreatment with 5 known carcinogens (termed DMBDD[b]) then 0, 50, 100, 200, 400 ppm DMA^V in the drinking-water during Week 6–30 Groups: DMBDD alone, DMBDD + 50 ppm DMA^V, DMBDD + 100 ppm DMA^V, DMBDD + 200 ppm DMA^V, DMBDD + 400 ppm DMA^V 20/group	Urinary bladder:[c]		Age at start, 7 wk DMA^V purity, 99%; DMA^V initially lowered but then increased bw; changes moderate and at high dose DMA^V increased water intake at high dose Survival unremarkable Separate 100 and 400 ppm (12 each) DMA^V alone groups were included but had no tumours or preneoplastic lesions
		Papillomas– 1/20 (5%), 12/20 (60%), 12/19 (63%), 11/20 (55%), 7/20 (35%)	$P < 0.01$ (three lowest) $P < 0.05$ (highest)	
		Transitional cell carcinomas– 1/20 (5%), 10/20 (50%), 11/19 (60%), 12/20 (60%), 13/20 (65%)	$P < 0.01$ (all DMA^V treatment groups)	
		Papillomas or carcinomas– 2/20 (10%), 17/20 (85%), 16/19 (84%), 17/20 (85%), 16/20 (80%)	$P < 0.01$ (all DMA^V treatment groups)	
		Kidney:		
		Adenomas– 1/20 (5%), 3/20 (15%), 1/19 (5%), 7/20 (35%), 3/20 (15%)	$P < 0.01$ (second highest)	
		Adenocarcinomas– 0/20, 0/20, 2/19 (10%), 1/20 (5%), 7/20 (35%)	$P < 0.01$ (high dose and trend)	
		Total– 5/20 (25%), 3/20 (15%), 6/19 (30%), 13/20 (65%), 13/20 (65%)	$P < 0.05$ (trend)	
		Liver:		
		Hepatocellular carcinomas– 0/20, 2/20 (10%), 0/19, 8/20 (40%), 8/20 (40%)	$P < 0.05$ (highest two and trend)	
		Total– 0/20, 2/20 (10%), 2/19 (10%), 17/20 (85%), 13/20 (65%)	$P < 0.05$ (highest two) $P < 0.01$ (trend)	
		Total thyroid gland tumours: 3/20 (15%), 2/20 (10%), 8/19 (40%), 6/20 (30%), 9/20 (45%)	$P < 0.05$ (highest) $P < 0.01$ (trend)	

Table 3.11 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M) 36 wk Wanibuchi *et al.* (1996)	Pretreatment with BBN[d] 0.05% in drinking-water for 4 wk then 0, 2, 10, 25, 50, or 100 ppm DMA^{V} in drinking-water for 32 wk Groups: BBN alone, BBN + 2 ppm DMA^{V}, BBN + 10 ppm DMA^{V}, BBN + 50 ppm DMA^{V}, BBN + 100 ppm DMA^{V} 20/group	Urinary bladder: Papillary/nodular hyperplasias– 14/20 (70%), 13/20 (65%), 14/20 (70%), 18/19 (95%), 20/20 (100%), 20/20 (100%) Papillomas– 3/20 (15%), 2/20 (10%), 7/20 (35%), 11/19 (58%), 13/20 (65%), 17/20 (85%) Carcinomas– 1/20 (5%), 2/20 (10%), 3/20 (15%), 7/19 (37%), 10/20 (50%), 12/20 (60%)	$P < 0.05$ (highest two doses) $P < 0.01$ (highest three doses) $P < 0.05$ (third highest dose) $P < 0.01$ (highest two doses)	Age at start, ~6 wk DMA^{V} purity, 99% Separate 0 and 100 ppm control and DMA^{V} alone groups were included (12 each) but showed no urinary bladder tumours or preneoplastic lesions Bw, water intake and survival unremarkable Urinary bladder only

[a] Diethylnitrosamine

[b] The organic carcinogen treatment consisted of a single dose of diethylnitrosamine (100 mg/kg, i.p.) at the start of the experiment) and*N*-methyl-*N*-nitrosourea (20 mg/kg, s.c.) on experimental Days 5, 8, 11 and 14. Thereafter, rats received 1,2-dimethylhydrazine (40 mg/kg, s.c.) on Days 18, 22, 26, and 30). During the same period (experimental Days 0–30) the rats received *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (0.05% in the drinking-water Weeks 1 and 2) and *N*-bis(2-hydroxypropyl)nitrosamine (0.1% in the drinking-water, Weeks 3 and 4). Altogether this was defined as DMBDD treatment. Rats received no treatment for 2 wk after DMBDD exposure and before DMA exposure.

[c] For brevity, only significant proliferative lesions are noted for each tissue

[d] *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine

[e] 4-Nitroquinoline

[f] 7,12-dimethylbenz[α]anthracene

[g] Estimated from graphical presentation.

d, day or days; DMA, dimethylarsinic acid; F, female; i.p., intraperitoneal; M, male; NR, not reported; s.c., subcutaneously; wk, week or weeks

Table 3.12 Studies where arsenicals given concurrently with other agents enhance carcinogenesis while having no effect alone in experimental animals

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Tg.AC homozygous (F) 14 wk Germolec *et al.* (1997)	0 or 0.02% As in drinking-water, *ad libitum* throughout experiment 0 or 2.5 µg TPA[a]/mouse in acetone topical to shaved dorsal skin twice/wk, Week 5 and 6 Groups: control, As alone, TPA, As + TPA 20/group	Macroscopic skin papillomas/mouse: none in control or arsenic alone, intermediate in TPA alone (~0.5/mouse),[b] "4-fold higher" (~2.1/mouse)[b] in arsenic + TPA	NR	Age at start, NR Purity, NR Survival unremarkable Specific quantitative microscopic analysis of skin tumours not included but confirmed as papillomas at termination Skin lesions only Incomplete reporting makes independent statistical analysis impossible
Mouse, Tg.AC homozygous (F) 24 wk Germolec *et al.* (1998)	0 or 0.02% As in drinking-water, *ad libitum* throughout experiment 0, 1.25, 2.5 µg TPA/mouse in acetone topical to shaved dorsal skin twice/wk, Week 5 and 6 Groups: control, As alone, 1.25 TPA, 2.5 TPA, As + 1.25 TPA, As + 2.5 TPA 20/group	Macroscopic skin papillomas/mouse: 0 in control, As alone, and 1.25 TPA alone; As + 1.25 TPA maximal ~5/mouse,[b] 2.5 TPA ~3/mouse,[b] in arsenic + 2.5 TPA ~7/mouse[b]	NR	Age at start, 8 wk Purity, NR Survival impacted by high-dose TPA co-treatment but specifics not given Quantitative microscopic analysis of skin tumours not included but confirmed as papillomas at termination Skin lesions only Incomplete reporting makes independent statistical analysis impossible

Table 3.12 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Crl: SKl-*hr*BR (hairless) (F) 29 wk Rossman *et al.* (2001)	0, 10 mg/L sodium arsenite in drinking-water throughout experiment plus topical 1.7 kJ/m² solar irradiation (85% UVB, < 1% UVC, 4% UVA, remainder visible; termed UVR[c]) 3x/wk starting 3 wk after As until termination Groups: control, As alone, UVR alone, As + UVR 5–15; 5 controls	Skin (tumours): Macroscopic and microscopic analysis–0/5, 0/5 (control and As alone) Macroscopic analysis– Time to first occurrence: As + UVR earlier than UVR Microscopic analysis– Total tumours all mice: 53 (UVR), 127 (As + UVR) Highly invasive squamous cell carcinoma: 14/53 (26%; UVR), 64/127 (50%; As + UVR) Tumour volume: UVR smaller than As + UVR	$P < 0.01$ $P < 0.01$ $P < 0.01$	Age at start, 3wk Purity, NR Survival and bw unremarkable Small control groups
Mouse, SKl (hairless), (NR) 29 wk Burns *et al.* (2004)	Experiment 1: 0, 1.25, 2.50, 5.00, 10.0 mg/L sodium arsenite in drinking-water from onset plus topical 0 or 1.0 kJ/m² solar irradiation (UVR[c]) 3x/wk, starting 3 wk after As to termination Experiment 2: 10.0 mg/L sodium arsenite in drinking-water from onset plus topical 1.7 kJ/m² UVR[c] 3x/wk starting 3 wk after As to termination	Experiment 1: Skin tumours/mouse[d]: 2.4 (UVR), 5.4 (1.25 As + UVR), 7.21 (2.5 As + UVR), 11.1 (5.0 As + UVR), 6.8 (10.0 As + UVR) Experiment 2: Skin tumours/mouse:[d] 3.5 (UVR), 9.6 (As + UVR) Skin tumour incidence: 0/10, 0/10 (control and As alone both experiments)	[$P < 0.01$ all groups vs UVR alone[e]] [$P < 0.01$[f]]	Age, 3 wk Survival and bw unremarkable Specific quantitative microscopic analysis of skin tumours not reported but confirmed as primarily squamous cell carcinomas at termination Experiment 1 shows clear arsenic dose–response in enhancement through 5.0 mg/L by various criteria

Table 3.12 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Crl: SKl-*hr*BR (hairless) (F) Duration, NR Uddin *et al.* (2005)	0, 5 mg/L sodium arsenite in drinking-water from onset; diet unsupplemented or with added vitamin E (62.5 IU/kg diet; basal 49.0 IU/kg) or *p*-XSC[g] (10 mg/kg diet) from onset. Topical 1.0 kJ/m^2 UVR[c] 3x/wk starting 3 wk after As to termination. Groups: UVR alone, UVR + As, UVR + As + Vitamin E, UVR + As + *p*-XSC[h] 10; 30 controls (UVR)	Macroscopic skin tumours/mouse: 3.60 (UVR alone), 7.00 (UVR + As), 3.27 (UVR + As + Vitamin E), 3.40 (UVR + As + *p*-XSC)	$P < 0.01$ (UVR vs UVR + As) $P < 0.01$ (UVR + As vs UVR + As + either dietary supplement)	Age at start, 3 wk Sodium arsenite, purity (NR), *p*-XSC Purity > 99% Survival and bw unremarkable Small control groups Vitamin E and *p*-XSC added as antioxidants Specific quantitative microscopic analysis of skin tumours not reported but random sampling (10 tumours/group) confirmed primarily squamous cell carcinomas at termination No untreated control or arsenic alone groups included
Mouse, Swiss-bald hairless (M) 25 wk Motiwale *et al.* (2005)	Treatment with 2 mg BA[i] /mL 25 µL topical once/wk for 2 wk Sodium arsenate 0 or 25 mg/L drinking-water for 25 wk Groups: Control, BA, As, BA + As 10/group	Macroscopic skin tumours/mouse: 0, 2.0, 0, 3.2[b] % large papillomas (≥ 3 mm) of total papillomas: 0, 16, 0, 65[d]	$P < 0.05$ (As + BA vs BA) $P < 0.05$ (As + BA vs BA)	Age at start, 8 wk Purity, NR Survival unremarkable Small group sizes Quantitative microscopic skin tumour incidence or multiplicity not reported though histologically confirmed

[a] 12-*O*-tetradecanoyl-13-acetate.
[b] Estimated from graphical presentation. No descriptive statistics included.
[c] UVR as defined in Rossman *et al.* (2001) above.
[d] Data included descriptive statistics.
[e] Using Dunnett's multiple comparison test and not including arsenic alone and untreated control groups
[f] Using Student's*t*-test.
[g] 1,4-Phenyl*bis*(methylene)selenocyanate a synthetic organoselenium compound.
[h] Some control groups are not discussed for the sake of brevity (UVR + Vitamin E and UVR +*p*-XSC).
[i] 9,10-dimethyl-1,2-benzanthracene.
F, female; M, male; NR, not reported; wk, week or weeks

of age, although arsenic treatment alone had no effect, it markedly increased the multiplicity of squamous cell carcinoma when combined with TPA compared to TPA alone (Waalkes *et al.*, 2008; see Table 3.13).

Prenatal sodium arsenite exposure via maternal drinking-water when combined with postnatal topical TPA exposure increased the liver tumour incidence and multiplicity in an arsenic-dose-related fashion (female offspring), and lung tumours (male offspring) compared to controls; effects not seen with TPA or arsenic alone (Waalkes *et al.*, 2004). Prenatal arsenic exposure followed by postnatal diethylstilbestrol increased uterine carcinoma, vaginal carcinoma, urinary bladder total proliferative lesions, and liver tumours in female offspring compared to controls; effects not seen with diethylstilbestrol or arsenic alone. In female offspring, prenatal arsenic exposure followed by postnatal tamoxifen administration similarly increased urinary bladder total proliferative lesions (Waalkes *et al.*, 2006a).

In male offspring, prenatal arsenic exposure followed by postnatal diethylstilbestrol increased the liver tumour response and urinary bladder total proliferative lesions effects when compared to controls; effects not seen with diethylstilbestrol or arsenic alone. In male offspring, prenatal arsenic exposure followed by postnatal tamoxifen increased liver tumour response, urinary bladder total tumours, and urinary bladder total proliferative lesions (Waalkes *et al.*, 2006b).

3.5.2 Rat

Rats that underwent partial hepatectomy followed by diethylnitrosamine injection and one week later by oral administration of sodium arsenite in the drinking-water for approximately 24 weeks showed an increased incidence of renal tumours, but arsenic treament alone had no effect (Shirachi *et al.*, 1983).

In a comprehensive study, rats were given an initial pretreatment with a mixture of organic carcinogens (including diethylnitrosamine, *N*-methyl-*N*-nitrosourea, 1,2-dimethylhydrazine, *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine, and *N*-bis(2-hydroxypropyl)nitrosamine) by various routes, no treatment for 2 weeks and then DMA^V (at four levels) in the drinking-water for 24 weeks, rats developed an increased incidence of tumours of urinary bladder with the combined carcinogen treatment and arsenical (Yamamoto *et al.*, 1995).

In another study in rats, *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine in the drinking-water was used as an initiator for 4 weeks followed by four levels of DMA^V for 32 weeks, and the combined treatment increased urinary bladder hyperplasia, papilloma, and carcinoma, but the arsenical treatment alone had no effect (Wanibuchi *et al.*, 1996).

3.6 Gallium arsenide

A single study (NTP, 2000) was judged to provide evidence for the carcinogenicity of gallium arsenide in rodents. In this report, $B6C3F_1$ mice and F344 rats were exposed via inhalation to various levels of gallium arsenide particulate for up to ~2 years, and the tumour response was assessed in various tissues (see Table 3.14).

3.6.1 Mouse

No treatment-related tumours were observed, but in both males and females, dose-related increases in the incidence in lung epithelial alveolar hyperplasia were reported.

3.6.2 Rat

In female rats, dose-related responses were reported for the incidence of lung alveolar/bronchiolar tumours and atypical hyperplasia

Table 3.13 Studies where arsenic given before another agent enhances carcinogenesis while having no effect alone in experimental animals

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Tg.AC (M, F) Homozygous 40 wk (*postpartum*) Waalkes *et al.* (2008)	Maternal exposure: 0, 42.5, 85 ppm arsenic in drinking-water, *ad libitum*, gestation Day 8–18	Skin (tumours): Papillomas/mouse[a]– 0.5 (control), 0.9 (42.5 As), 0.12 (85 As), 17 (TPA[b]), 17 (42.5 As + TPA), 11 (85 As + TPA)	$P < 0.05$ (all TPA groups vs control; TPA alone vs 85As + TPA)	Age, 4 wk (offspring) Purity, NR Litters culled at 4 d *postpartum* to no more than 8 pups 10 pregnant mice used to randomly derive each group Maternal water consumption and body unaltered Offspring weaned at 4 wk Offspring bw unaltered by arsenic All skin tumours were histopathologically diagnosed for stage and number per animal Some mice were killed because of tumour burden during experiment but were not lost to observation Only skin tumours reported
	Offspring exposure:[a] TPA, 2 µg/0.1 mL acetone, topical twice/wk, applied to shaved dorsal skin, 4–40 wk of age (36 wk of TPA exposure)	Squamous cell carcinomas/mouse:[a] 0.04 (control), 0.06 (42.5 As), 0.04 (85 As), 0.57 (TPA), 1.31 (42.5 As + TPA), 1.49 (85 As + TPA)	$P < 0.05$ (all TPA groups vs control; all As + TPA groups vs TPA alone $P < 0.01$ (trend with As in TPA-treated mice)	
	Offspring groups (M, F):[c] Without TPA: (0, 42.5, 85 ppm arsenic) With TPA: (0, 42.5, 85 ppm arsenic) 50/group	Incidence of mice with 3 or more squamous cell carcinomas: 0/49 (control), 0/47 (42.5 As), 0/48 (85 As), 1/47 (2%; TPA), 9/48 (19%; 42.5 As + TPA), 14/49 (29%; 85 As + TPA)	$P < 0.05$ (all TPA + As groups vs control or TPA alone) $P < 0.01$ (trend with As in TPA-treated mice)	

[a] Manuscript included descriptive statistics.
[b] 12-*O*-tetradecanoyl-13-acetate.
[c] Because initial analysis of tumours showed no gender-based differences between similarly treated groups of males and females, they were pooled for final assessment and are reported as such. Initial groups were made up of 25 M and 25 F mice.
bw, body weight; F, female; M, male; NR, not reported; vs; versus; wk, week or weeks

Table 3.14 Studies of cancer in experimental animals exposed to gallium arsenide (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 105 wk for M 106 wk for F NTP (2000)	0, 0.1, 0.5, 1.0 mg/m^3 6 h/d, 5 d/wk 50/group/sex	**Females** Lung (epithelial alveolar hyperplasias):2/50 (4%), 5/50 (10%), 27/50 (54%), 43/50 (86%) Lung[a] (adenomas or carcinomas): 7/50 (14%), 4/50 (8%), 4/50 (8%), 6/50 (12%) **Males** Lung (epithelial alveolar hyperplasias):4/50 (8%), 9/50 (18%), 39/50 (78%), 45/50 (90%) Lung[a] (adenomas or carcinomas): 15/50 (30%), 14/50 (28%), 16/50 (32%), 13/50 (26%)	$P \leq 0.01$ (high dose) $P \leq 0.01$ (mid-dose) NS $P \leq 0.01$ (high dose) $P \leq 0.01$ (mid-dose) NS	Age at start, 6 wk Purity > 98% MMAD, 0.9–1.0 µm GSD, 1.8–1.9 µm Chamber controls used No reduced bw with treatment Survival unaltered No increases in tumour incidence
Rat, F344 (F) 105 wk NTP (2000)	0, 0.01, 0.1, 1.0 mg/m^3 6 h/d, 5 d/wk 50/group/sex	**Females** Lung[a] (adenomas): 0/50, 0/50, 2/50 (4%), 7/50 (14%) Lung (carcinomas): 0/50, 0/50, 2/50 (4%), 3/50 (6%) Lung (adenomas or carcinomas): 0/50, 0/50, 4/50 (8%), 9/50 (18%) Adrenal medulla:[b] 4/50 (8%), 6/49 (12%), 6/50 (12%), 13/49 (27%) Mononuclear cell leukaemia: 22/50 (44%), 21/50 (42%), 18/50 (36%), 33/50 (66%) **Males** Lung (atypical hyperplasias): 0/50, 2/49 (4%), 5/50 (10%), 18/50 (36%) Lung[a] (adenomas): 1/50 (2%), 0/49, 3/50 (6%), 2/50 (4%) Lung (carcinomas): 2/50 (4%), 0/49, 2/50 (4%), 1/50 (2%) Lung (adenomas or carcinomas): 3/50 (6%), 0/49, 5/50 (10%), 3/50 (6%)	$P \leq 0.01$ (high dose) $P \leq 0.01$ (trend) NS $P \leq 0.01$ (high dose) $P \leq 0.01$ (trend) $P \leq 0.01$ (high dose) $P \leq 0.01$ (trend) $P \leq 0.05$ (high dose) $P \leq 0.01$ (trend) $P \leq 0.01$ (high dose) $P \leq 0.05$ (mid-dose) NS NS NS	Age at start, 6 wk Purity > 98% MMAD, 0.9–1.0 µm GSD, 1.8–1.9 µm Chamber controls used Minimal decrease in body weight at high dose in second yr Survival unaltered No increases in tumour incidence in males

[a] All lung tumours were of avelolar/bronchiolar origin.
[b] All tumours were benign pheochromocytoma except one which was malignant in the low-dose group.
d, day or days; F, female; h, hour or hours; M, male; NS, not significant; wk, week or weeks; yr, year or years

of the alveolar epithelium. In male rats, though treatment-related tumours were not observed, a dose-related increase in the incidence of atypical hyperplasia of the lung alveolar epithelium occurred. Atypical hyperplasia of the lung alveolar epithelium is considered potentially preneoplastic. In the female rats, dose-related increases in the incidence of adrenal medulla pheochromocytomas and an increase in mononuclear cell leukaemia at the highest dose were also reported (NTP, 2000).

3.6.3 Hamster

Another study using intratracheal instillation of gallium arsenide in hamsters (Ohyama *et al.*, 1988) was judged inadequate due to critical design flaws (short duration, small groups, etc.) with no indication of tumours.

3.7 Synthesis

Oral administration of sodium arsenate and DMA^V induced lung tumours in mice. Calcium arsenate induced lung tumours in hamsters by oral and intratracheal administration. Pre- and postnatal exposure in mice to arsenic trioxide, through subcutaneous injections (maternal and postnatal), induced lung tumours in the offspring. Transplacental exposure via maternal oral exposure in mice to sodium arsenite during gestation induced lung, liver, ovary and adrenal tumours in the offspring in several studies, and the uterus in one study. Early life transplacental and perinatal exposure to sodium arsenite appears to be a time of particular sensitivity in terms of carcinogenesis.

Oral exposure to DMA^V induced urinary bladder tumours in several studies in rats and among studies in mice, only one showed negative results. Oral trimethylarsine induced liver tumours in rats. Chronic oral exposure to MMA^V did not produce tumours in rats and mice. [The Working Group considered that previous traditional bioassays for arsenicals for adult rodents were frequently negative in their final evaluations.]

Inhalation of gallium arsenide causes lung and adenal tumours in rats but not in mice.

In multiple studies, initiating, promoting or co-carcinogenic activity was demonstrated in the urinary bladder, skin, female reproductive tract, kidney, lung, liver and thyroid after exposure to inorganic arsenicals or DMA^V in drinking-water or by transplacental exposure.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

Most inorganic arsenic compounds are readily absorbed after oral exposure (about 80–90% for soluble compounds, and a smaller percentage for less soluble compounds), less well absorbed after inhalation (better for small particulates and soluble arsenicals), and least well absorbed after dermal exposure (NRC, 1999; IARC, 2004). Large airborne arsenic-containing particulates that are deposited in the upper airways may also be absorbed in the intestine if they are later swallowed. Hamsters exposed to gallium arsenide by the oral route or by intratracheal instillation showed the presence of As^{III} in blood and urine, but the majority of the gallium arsenide was excreted in faeces, indicating that absorption was limited by its insolubility. Absorption was about 30 times higher after intratracheal installation than by the oral route (Carter *et al.*, 2003).

The transport of As^V is thought to take place via phosphate transporters (Csanaky & Gregus, 2001). The sodium-coupled phosphate transporter NaPi-IIb may be responsible in part for the intestinal and hepatic uptake of As^V (Villa-Bellosta & Sorribas, 2008). As^{III} enters the cell by aquaglyceroporins 9 and 7 (Liu *et al.*, 2004),

although another major pathway for the uptake of As^{III} and MMA^{III} (see below) is probably via hexose permeases (Rosen & Liu, 2009). Because As^{V} is rapidly reduced to As^{III} once it enters the cell (Carter *et al.*, 2003), the faster rate of cellular uptake of As^{III}, compared with As^{V}, may be part of the explanation for the greater toxicity of As^{III} (Bertolero *et al.*, 1987; Dopp *et al.*, 2004). However, the much higher chemical reactivity of As^{III}, compared to that of As^{V} is the major explanation. Some data suggests that glyceraldehyde 3-phosphate dehydrogenase (GAPDH) functions as a cytosolic As^{V} reductase *in vivo* (Németi *et al.*, 2006), although there are other candidate enzymes for this reaction (Aposhian *et al.*, 2004). As^{III} can react with cellular glutathione (GSH), either spontaneously or enzymatically, to form the tri-glutathione complex $As(SG)_3$ (Leslie *et al.*, 2004; Rey *et al.*, 2004).

As^{III} is metabolized by stepwise methylation, mainly in the liver. Although some details of inorganic arsenic metabolism remain uncertain (Aposhian & Aposhian, 2006), it is clear that the enzyme arsenic (+3 oxidation state) methyltransferase (AS3MT) is involved (Thomas *et al.*, 2007). Two schemes have been proposed for the methylation.

Reduction: As^{V} + thiol → As^{III}
Oxidative methylation: As^{III} + SAM → monomethylarsonate (MMA^{V})
Reduction: MMA^{V} + thiol → MMA^{III}
Oxidative methylation: MMA^{III} + SAM → dimethylAs^{V} (DMA^{V})
Reduction: DMA^{V} + thiol → DMA^{III}

Scheme 1: Inorganic arsenic metabolic pathway in mammals. As^{III} methylation is catalysed by AS3MT using *S*-adenosylmethionine (SAM) as a methyl donor and thioredoxin (or, less efficiently, other thiols such as glutaredoxin or lipoic acid) as a reductant. MMA^{III}: monomethylarsonous acid; MMA^{v}: monomethylarsonic acid; DMA^{III}: dimethylarsinous acid; DMA^{v}: dimethylarsinic acid

$As(SG)_3$ + SAM → $MMA^{III}(SG)_2$
$MMA^{III}(SG)_2$ + SAM → $DMA^{III}(SG)$

Scheme 2: The use of $As(SG)_3$ (tri-glutathione complex) as a substrate for methylation (Hayakawa *et al.*, 2005). Each of the glutathione (GSH) complexes can also decompose to yield GSH and MMA^{III} or DMA^{III}, which can then form MMA^{V} and DMA^{V}, respectively.

Neither reaction scheme necessarily goes to completion *in vivo*.

Evidence shows that exposure to arsine gas (AsH_3) results in the same metabolites as described above, but arsenobetaine found in seafood does not get metabolized in humans (Crecelius, 1977; Luten *et al.*, 1982; Le *et al.*, 1993, 1994; Buchet *et al.*, 1996; Schmeisser *et al.*, 2006). Information is not currently available on the other organo-arsenic compounds in seafood (Lai *et al.*, 2004).

Dimethylthioarsinic acid ($DMMTA^{V}$) and dimethyldithioarsinic acid ($DMDTA^{V}$) can be formed from DMA^{III} in red blood cells, and possibly in other cells (Naranmandura *et al.*, 2007; Suzuki *et al.*, 2007). These compounds have been observed in the urine of arsenic-exposed individuals (Raml *et al.*, 2007). They may have been misidentified as MMA^{III} and DMA^{III} in most studies (Hansen *et al.*, 2004).

Most organisms detoxify inorganic arsenic by cellular efflux (Rosen & Liu, 2009). In fibroblasts and other non-methylating cells, protection against arsenic takes place by specific mechanisms for $As(SG)_3$ efflux catalysed by multidrug-resistance-associated protein-transport ATPases MRP1 and MRP2, and maybe others (Kala *et al.*, 2000; Leslie *et al.*, 2004). These efflux pumps may also remove methylated arsenic–glutathione (As–GSH) complexes.

The rat is not a good model for the human in studying the toxicokinetics of arsenic because rat haemoglobin has a much higher affinity for trivalent arsenic species compared with human haemoglobin (Lu *et al.*, 2004). In mice, chronic

exposure (12 weeks) to As^{V} via drinking-water led to total tissue arsenic accumulation in the following ranking: kidney > lung > bladder > > > skin > blood > liver (Kenyon *et al.*, 2008). Monomethylated arsenic species (MMAs) predominated in the kidney, and dimethylated arsenic species (DMAs) predominated in the lung. Urinary bladder and skin had about equal ratios of inorganic arsenic and DMAs. The proportions of different arsenic species in urinary bladder tissue did not match those in urine.

In a study of intratracheal instillation of gallium arsenide, although substantial levels of arsenic were detected in blood and urine, no gallium was detected except for the amount that was left in the lung (Carter *et al.*, 2003).

Human exposure to arsenic is mainly via drinking-water. Trivalent arsenicals are eliminated via the bile, and pentavalent arsenicals are mainly eliminated by urinary excretion (Gregus *et al.*, 2000; Kala *et al.*, 2000; Csanaky & Gregus, 2002). Most population groups exposed mainly via drinking-water excrete 60–70% DMAs and 10–20% MMAs, the remainder 10–30% being inorganic compounds (Vahter, 2000). [The Working Group noted that this study did not include thiolated compounds, which had not yet been discovered.] Interindividual differences in methylation patterns may reflect genetic polymorphisms in AS3MT, and/or variability in the activities of different reductants (Thomas *et al.*, 2007).

4.2 Genetic and related effects

Arsenicals do not react directly with DNA, but cells treated with low concentrations of trivalent arsenicals show increased oxidative DNA damage (Wang *et al.*, 2002; Schwerdtle *et al.*, 2003; Shi *et al.*, 2004; Ding *et al.*, 2005; Wang *et al.*, 2007a). As^{III} and MMA^{III} are equally potent inducers of oxidative DNA damage in human urothelial cells, where they are equally toxic (Wang *et al.*, 2007a). Cytotoxic concentrations of trivalent arsenicals also cause DNA strand breaks and/or alkali-labile sites (Kligerman *et al.*, 2003; Klein *et al.*, 2007). In mice, DMA^{V} causes lung-specific DNA damage attributed to the DMA peroxy radical $(CH_3)_2AsOO$ (Yamanaka & Okada, 1994), which can also induce DNA strand breaks and DNA–protein crosslinks in cultured cells (Tezuka *et al.*, 1993).

Gallium arsenide and other arsenicals are not mutagenic in the Ames test (NTP, 2000; IARC, 2004). There was no increase in frequency of micronucleated erythrocytes in mice exposed to gallium arsenide by inhalation for 14 weeks (NTP, 2000).

Despite the fact that low (non-toxic) concentrations of trivalent arsenicals cause oxidative DNA damage such as 8-hydroxy-2′-deoxyguanosine, which is expected to cause G→T transversions, neither As^{III}, MMA^{III} nor DMA^{III} are significant point mutagens (Rossman, 2003; Klein *et al.*, 2007). This may be due to the efficient removal of oxidative DNA lesions (Fung *et al.*, 2007; Pu *et al.*, 2007b). At toxic concentrations, As^{III} increased large-deletion mutations in human/hamster hybrid cells through a mechanism mediated by reactive oxygen species (Hei *et al.*, 1998). MMA^{III} and DMA^{III} are weakly mutagenic in mouse lymphoma L5178Y cells, but only at toxic concentrations, and yield mostly deletions (Moore *et al.*, 1997; Kligerman *et al.*, 2003).

Using a transgenic cell line that readily detects deletions as well as point mutations, statistically significant mutagenesis was never observed for DMA^{III}, and was only seen for As^{III} or MMA^{III} at toxic concentrations. MMA^{III} yielded a mutant fraction about 4-fold over background at 11% survival, and 79% of these mutants were deletions (Klein *et al.*, 2007).

As^{III}, MMA^{III}, and DMA^{III} can induce chromosomal aberrations *in vitro* (Oya-Ohta *et al.*, 1996; Kligerman *et al.*, 2003). Statistically significant increases in chromosomal aberrations occur only at toxic doses (Klein *et al.*, 2007), except as a secondary effect of genomic

instability in long-term, low-dose treatment protocols (Sciandrello *et al.*, 2004). An analysis of micronuclei induced by As^{III} in human fibroblasts shows that at lower (relatively non-toxic) doses, As^{III} acts as an aneugen by interfering with spindle function and causing micronuclei with centromeres, but at high (toxic) doses, it acts as a clastogen, inducing micronuclei without centromeres (Yih & Lee, 1999). Aneuploidy is seen after treatment with As^{III} concentrations lower than those that cause chromosomal aberrations (Yih & Lee, 1999; Ochi *et al.*, 2004; Sciandrello *et al.*, 2002, 2004). Aneuploidy associated with disruption of spindle tubulin has been reported in other cells treated with arsenicals (Huang & Lee, 1998; Kligerman & Tennant, 2007; Ramírez *et al.*, 2007). Disrupted mitotic spindles and induced persistent aneuploidy were maintained even 5 days after As^{III} removal (Sciandrello *et al.*, 2002). Humans exposed to high concentrations of inorganic arsenic in drinking-water also show increased micronuclei in lymphocytes, exfoliated bladder epithelial cells and buccal mucosa cells, and sometimes chromosomal aberrations and sister chromatid exchange in whole-blood lymphocyte cultures (Basu *et al.*, 2001). Micronuclei and chromosomal aberrations are also induced in mice after intraperitoneal treatment with As^{III} (IARC, 2004).

Long-term low-dose treatment of human osteosarcoma cells with As^{III} (but not MMA^{III}) resulted in increased mutagenesis and transformation as a secondary effect of genomic instability (Mure *et al.*, 2003). In Chinese hamster V79–13 cells grown in the presence of low concentrations of As^{III}, genomic instability (measured by chromosomal aberrations in later generations) followed earlier changes in DNA methylation and aneuploidy (Sciandrello *et al.*, 2002, 2004). Other studies report gene amplification (Lee *et al.*, 1988; Rossman & Wolosin, 1992), and changes in gene expression, e.g. by DNA methylation changes (Liu *et al.*, 2006b; Klein *et al.*, 2007; Reichard *et al.*, 2007; Liu & Waalkes, 2008). Alterations of DNA methylation, along with histone modification, were seen in cells treated with As^{III} and MMA^{III} (Jensen *et al.*, 2008; Zhou *et al.*, 2008). Global DNA hypomethylation, along with hypermethylation of specific genes, was demonstrated in several As^{III}-transformed cells (Benbrahim-Tallaa *et al.*, 2005a; Liu & Waalkes, 2008). Oxidative damage to DNA has been shown to cause changes in DNA methylation (Cerda & Weitzman, 1997), suggesting a mechanism by which As^{III} may induce this effect. Changes in DNA methylation patterns could also result from altered SAM pools or downregulation of DNA methyltransferases (Hamadeh *et al.*, 2002; Benbrahim-Tallaa *et al.*, 2005a; Reichard *et al.*, 2007; Liu & Waalkes, 2008). Altered DNA methylation has also been observed in arsenic-exposed humans (Chanda *et al.*, 2006; Marsit *et al.*, 2006).

Although not a mutagen, As^{III} can enhance the mutagenicity of other agents (Rossman, 2003; Danaee *et al.*, 2004; Fischer *et al.*, 2005). Co-mutagenesis may occur by interference with both nucleotide-excision repair and base-excision repair (Hartwig *et al.*, 2002; Rossman, 2003; Danaee *et al.*, 2004; Wu *et al.*, 2005; Shen *et al.*, 2008). Nucleotide-excision repair was blocked in human fibroblasts with the following potency: $MMA^{III} > DMA^{III} > As^{III}$ (Shen *et al.*, 2008). As^{III} is not a very effective inhibitor of DNA-repair enzymes (Snow *et al.*, 2005). Rather, it appears to affect DNA-damage signalling events that control DNA repair. One of these is poly(ADP-ribose) polymerase (PARP) (Hartwig *et al.*, 2003; Qin *et al.*, 2008). PARP-1, the major PARP, is involved in base-excision repair by interacting with DNA-repair protein XRCC1, DNA polymerase β, and DNA ligase ^{III}. This might explain the inhibition of the ligation step of base-excision repair by As^{III} (Li & Rossman, 1989). MMA^{III} and DMA^{III} are more effective PARP inhibitors than is As^{III} (Walter *et al.*, 2007). The inhibition of PARP (and other proteins such as XPA) may be

mediated by the displacement of zinc (Zn) at Zn fingers (Schwerdtle *et al.*, 2003; Qin *et al.*, 2008).

Another important signal pathway affected by As^{III} is that mediated by tumour-suppressor gene *Tp53*. As^{III} was shown to prevent the activation of the P53 protein and the downstream expression of p21 after genotoxic insult (Vogt & Rossman, 2001; Tang *et al.*, 2006; Shen *et al.*, 2008). This has the effect of overriding the growth arrest at G1 (normally an opportunity for DNA repair to take place before DNA replication) in cells with DNA damage, and might explain part of the co-mutagenic effect (Vogt & Rossman, 2001; Hartwig *et al.*, 2002; Mudipalli *et al.*, 2005). p53 is also required for proficient global nucleotide-excision repair (Ferguson & Oh, 2005). The inhibition of thioredoxin reductase by As^{III}, MMA^{III} and DMA^{III} (Lin *et al.*, 1999) would cause the accumulation of oxidized thioredoxin, which may be partially responsible for p53 malfunction, as is shown in yeast (Merwin *et al.*, 2002). The upregulation of positive growth genes such as cyclin D by low concentrations of As^{III} would also tend to drive cells to cycle inappropriately (Trouba *et al.*, 2000; Vogt & Rossman, 2001; Luster & Simeonova, 2004).

In addition to inhibiting particular proteins, As^{III} (at slightly toxic concentrations) can down-regulate expression of some DNA repair genes (Hamadeh *et al.*, 2002; Andrew *et al.*, 2006; Sykora & Snow, 2008). However, very low, non-toxic concentrations, may have the opposite effect of upregulating DNA repair, concomitant with antioxidant defenses (Snow *et al.*, 2005; Sykora & Snow, 2008).

4.3 Co-carcinogenic and *in utero* carcinogenic effects

There are several non-genotoxic actions of As^{III} (sometimes demonstrated also for its trivalent metabolites) that may contribute to arsenic-induced carcinogenesis. The effects of As^{III} on preventing blockage of the cell cycle after genotoxic insult by a second agent were discussed above. In addition, low concentrations of As^{III} in the absence of a second agent can also stimulate cell proliferation *in vitro* (Germolec *et al.*, 1997; Trouba *et al.*, 2000; Vogt & Rossman, 2001; Benbrahim-Tallaa *et al.*, 2005b; Komissarova *et al.*, 2005), and *in vivo* (Germolec *et al.*, 1998; Burns *et al.*, 2004; Luster & Simeonova, 2004). The concentration-dependent increase in proliferation of human keratinocytes after 24 hours of treatment with arsenicals followed the potency trend: $DMA^{III} > MMA^{III} > As^{III}$ (Mudipalli *et al.*, 2005). As^{III} upregulates pro-growth proteins such as cyclin D1, c-myc, and E2F-1 (Trouba *et al.*, 2000; Vogt & Rossman, 2001; Ouyang *et al.*, 2007). The increased proliferation in mouse skin by As^{III} alone (in drinking-water) is not sufficient to induce skin cancer (Burns *et al.*, 2004), but may contribute to its co-carcinogenesis with solar ultraviolet. As^{III} was found to block the differentiation of skin cells, resulting in increased numbers of keratinocyte stem cells, the cells that proliferate (Patterson & Rice, 2007; Waalkes *et al.*, 2008). Because tumours may arise from stem cells, this would increase the pool of target cells for cancer of the skin.

Another mechanism for arsenic-related carcinogenesis might be acquired resistance to apoptosis. Long-term growth of human skin cells (HaCaT) in the presence of low concentrations of As^{III} resulted in cells with a generalized resistance to apoptosis (Pi *et al.*, 2005). This may allow the survival of cells with DNA damage, thus facilitating tumorigenesis. Even short-term exposure to As^{III} affected the apoptotic response to solar UV in a mouse keratinocyte cell line (Wu *et al.*, 2005) or to UVB in normal human keratinocytes (Chen *et al.*, 2005b). It is possible that the loss of the P53 function partially mediates the reduction in apoptotic response (Chen *et al.*, 2005b).

Numerous studies report increased inflammation after As^{III} exposure (NRC, 1999; Straub

et al., 2007). The transcription factor NF-κB is involved in the inflammatory response, and As^{III} causes oxidant-dependent activation of NF-κB (Barchowsky *et al.*, 1999). Activation of the NF-κB inflammatory signalling pathway was seen in infants born to As^{III}-exposed mothers in Bangladesh (Fry *et al.*, 2007).

As^{III} can disrupt the signalling of the estrogen receptor, glucocorticoid receptor, and of other steroids *in vivo* and *in vitro* (Benbrahim-Tallaa *et al.*, 2005b, 2007; Liu *et al.*, 2007; Davey *et al.*, 2008). Submicromolar concentrations of As^{III} stimulate the transcription of several steroid receptors, but slightly higher concentrations (1–3 μM) are inhibitory (Bodwell *et al.*, 2006). Exposure of mice *in utero* to As^{III} in a protocol leading to hepatocarcinogenesis resulted in altered expression of numerous genes involved in estrogen signalling or steroid metabolism, as well as hypomethylation of estrogen receptor α (Liu & Waalkes, 2008).

Angiogenesis, which provides a blood supply to developing tumours, is stimulated by very low concentrations of As^{III} (Mousa *et al.*, 2007; Straub *et al.*, 2007). This activity can be blocked by selenium compounds (Mousa *et al.*, 2007), which also blocks As^{III}-induced co-carcinogenesis with UV and delays mutagenesis (Uddin *et al.*, 2005).

Many of these effects depend on altered gene expression that can result from genetic and epigenetic effects discussed above. Changes in gene expression by As^{III} can also be mediated by the alteration of miRNA patterns (Marsit *et al.*, 2006). Some short-term changes in gene expression (e.g. changes in the expression of DNA-repair proteins or DNA methyltransferases) can result in long-term changes. Genome-wide changes in gene expression and signal transduction induced by arsenicals have been reported in several publications (Su *et al.*, 2006; Kumagai & Sumi, 2007; Ghosh *et al.*, 2008).

4.4 Synthesis

In the human body, inorganic arsenic compounds are converted to As^{III} and As^{V}. As^{V} is rapidly converted to As^{III}. As^{III} species are more toxic and bioactive than are As^{V} species, both because of the greater chemical reactivity of As^{III}, and because As^{III} enters cells more easily.

For inorganic arsenic and its metabolites, the evidence points to weak or non-existent direct mutagenesis, which is seen only at highly cytotoxic concentrations. On the other hand, long-term, low-dose exposure to inorganic arsenic – more relevant to human exposure – is likely to cause increased mutagenesis as a secondary effect of genomic instability, perhaps mediated by increased levels of reactive oxygen species, as well as co-mutagenesis with other agents. The major underlying mechanisms observed at low concentrations include the rapid induction of oxidative DNA damage and DNA-repair inhibition, and slower changes in DNA-methylation patterns, aneuploidy, and gene amplification. Gene amplification, altered DNA methylation, and aneuploidy lead to altered gene expression, and genomic instability. Inhibition of DNA repair leads to co-mutagenicity as well. These effects are consistent with the animal carcinogenicity data, in which As^{III} is a transgenerational carcinogen – with exposure being present during many cell generations – and in results observed in co-carcinogenicity studies.

For bladder tumours induced by high doses of DMA^{V} in the rat, the mechanism is likely to involve sustained cytotoxicity followed by stress-related cell proliferation, leading to genomic instability.

Inflammation and cytotoxicity may play a role in lung tumours induced by gallium arsenide in female rats.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of mixed exposure to inorganic arsenic compounds, including arsenic trioxide, arsenite, and arsenate. Inorganic arsenic compounds, including arsenic trioxide, arsenite, and arsenate, cause cancer of the lung, urinary bladder, and skin. Also, a positive association has been observed between exposure to arsenic and inorganic arsenic compounds and cancer of the kidney, liver, and prostate.

There is *sufficient evidence* in experimental animals for the carcinogenicity of dimethylarsinic acid, calcium arsenate, and sodium arsenite.

There is *limited evidence* in experimental animals for the carcinogenicity of sodium arsenate, gallium arsenide, arsenic trioxide, and trimethylarsine oxide.

There is *inadequate evidence* in experimental animals for the carcinogenicity of monomethylarsonic acid and arsenic trisulfide.

In view of the overall findings in animals, there is *sufficient evidence* in experimental animals for the carcinogenicity of inorganic arsenic compounds.

Arsenic and inorganic arsenic compounds are *carcinogenic to humans (Group 1).*

Dimethylarsinic acid and monomethylarsonic acid are *possibly carcinogenic to humans (Group 2B).*

Arsenobetaine and other organic arsenic compounds not metabolized in humans, are *not classifiable as to their carcinogenicity to humans (Group 3).*

The Working Group made the overall evaluation on 'arsenic and inorganic arsenic compounds' rather than on some individual arsenic compounds, based on the combined results of epidemiological studies, carcinogenicity studies in experimental animals, and data on the chemical characteristics, metabolism, and modes of action of carcinogenicity.

Elemental arsenic and inorganic arsenic species share the same metabolic pathway: arsenate→arsenite→methylarsonate→dimethylarsenite. Thus, independent of the mechanisms of the carcinogenic action, and independent of which of the metabolites is the actual ultimate carcinogen, different inorganic arsenic species should be considered as carcinogenic.

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BERYLLIUM AND BERYLLIUM COMPOUNDS

Beryllium and beryllium compounds were considered by previous IARC Working Groups in 1971, 1979, 1987, and 1993 (IARC, 1972, 1980, 1987, 1993). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms and molecular formulae for beryllium, beryllium–aluminium and beryllium–copper alloys, and certain beryllium compounds are presented in Table 1.1. The list is not exhaustive, nor does it comprise necessarily the most commercially important beryllium-containing substances; rather, it indicates the range of beryllium compounds available.

1.2 Chemical and physical properties of the agents

Beryllium (atomic number, 4; relative atomic mass, 9.01) is a metal, which belongs to Group IIA of the Periodic Table. The oxidation state of beryllium compounds is +2. Selected chemical and physical properties of beryllium, beryllium–aluminium and beryllium–copper alloys, and various beryllium compounds can be found in the previous *IARC Monograph* (IARC, 1993).

Beryllium is the lightest of all solid chemically stable substances, and has an unusually high melting-point. It has a very low density and a very high strength-to-weight ratio. Beryllium is lighter than aluminium but is greater than 40% more rigid than steel. It has excellent electrical and thermal conductivities. Its only markedly adverse feature is relatively pronounced brittleness, which restricts the use of metallic beryllium to specialized applications (WHO, 1990).

Because of its low atomic number, beryllium is very permeable to X-rays. Neutron emission after bombardment with α or γ rays is the most important of its nuclear physical properties, and beryllium can be used as a neutron source. Moreover, its low neutron absorptiveness and high-scattering cross-section make it a suitable moderator and reflector in structural materials in nuclear facilities; where most other metals absorb neutrons emitted during the fission of nuclear fuel, beryllium atoms only reduce the energy of such neutrons, and reflect them back into the fission zone (Ballance *et al.*, 1978; Newland, 1984; WHO, 1990).

The chemical properties of beryllium differ considerably from those of the other alkaline earths, but it has several chemical properties in common with aluminium. Like aluminium, beryllium is amphoteric and shows very high affinity for oxygen; on exposure to air or water vapour, a thin film of beryllium oxide forms on

Table 1.1 Chemical names (CAS names are in italics), CAS numbers, synonyms, and molecular formulae of beryllium and beryllium compounds

Chemical name	CAS Reg. No[a]	Synonyms	Formula
Beryllium metal	7440-41-7	*Beryllium*; beryllium element; beryllium metallic	Be
Beryllium–aluminum alloy[b]	12770-50-2	*Aluminium alloy, nonbase, Al,Be*; aluminium–beryllium alloy	Al.Be
Beryllium–copper alloy[c]	11133-98-5	*Copper alloy, base, Cu,Be*; copper–beryllium alloy	Be.Cu
Beryl	1302-52-9	Beryllium aluminosilicate; beryllium aluminium silicate	$Al_2Be_3(SiO_3)_6$
Beryllium chloride	7787-47-5	Beryllium dichloride	$BeCl_2$
Beryllium fluoride	7787-49-7 (12323-05-6)	Beryllium difluoride	BeF_2
Beryllium hydroxide	13327-32-7 (1304-49-0)	Beryllium dihydroxide	$Be(OH)_2$
Beryllium sulfate	13510-49-1	*Sulfuric acid, beryllium salt (1:1)*	$BeSO_4$
Beryllium sulfate tetrahydrate	7787-56-6	*Sulfuric acid, beryllium salt (1:1), tetrahydrate*	$BeSO_4.4H_2O$
Beryllium oxide	1304-56-9	Beryllia; beryllium monoxide	BeO
Beryllium carbonate basic[d]	1319-43-3	*Carbonic acid, beryllium salt, mixture with beryllium hydroxide ($Be(OH)_2$)*	$BeCO_3.Be(HO)_2$
Beryllium nitrate	13597-99-4	Beryllium dinitrate; *nitric acid, beryllium salt*	$Be(NO_3)_2$
Beryllium nitrate trihydrate	7787-55-5	*Nitric acid, beryllium salt, trihydrate*	$Be(NO_3)_2.3H_2O$
Beryllium nitrate tetrahydrate	13510-48-0	Beryllium dinitrate tetrahydrate; *nitric acid, beryllium salt, tetrahydrate*	$Be(NO_3)_2.4H_2O$
Beryllium phosphate	13598-15-7	*Phosphoric acid, beryllium salt (1:1)*	$BeHPO_4$
Beryllium silicate[e]	13598-00-0	Phenazite; *phenakite*	$Be_2(SiO_4)$
Zinc beryllium silicate	39413-47-3 (63089-82-7)	*Silicic acid, beryllium zinc salt*	Unspecified

[a] Replaced CAS Registry numbers are shown in parentheses.

[b] Related compound registered by CAS is beryllium alloy, base, Be, Al historically (Lockalloy), Al (24–44%).Be (56–76%) [12604-81-8; replaced Registry No., 12665-28-0]; 60 beryllium–aluminium alloys are registered with CAS numbers, with different percentages of the two elements.

[c] Related compound registered by CAS is beryllium alloy, base, Be,Cu [39348-30-6]; 111 beryllium–copper alloys are registered with CAS numbers, with different percentages of the two elements.

[d] CAS name and Registry number shown were selected as being closest to the formula given by Lide (1991). Related compounds registered by CAS are: bis[carbonato(2)]dihydroxytriberyllium, $(BeCO_3)2.Be(OH)_2$ [66104-24-3]; carbonic acid, beryllium salt (1:1), tetrahydrate, $BeCO_3.4H_2O$ [60883-64-9]; carbonic acid, beryllium salt (1:1), $BeCO_3$ [13106-47-3]; and bis[carbonato(2-)]oxodiberyllium, $(CO_3)2Be_2O$ [66104-25-4].

[e] Related compounds registered by CAS are: bertrandite, $Be_4(OH)_2O(SiO_3)_2$ [12161-82-9]; beryllium silicate, formula unspecified [58500-38-2]; silicic acid (H_2SiO_3), beryllium salt (1:1), $Be(SiO_3)$ [14902-94-4]; silicic acid (H_4SiO_4), beryllium salt (1:2), $Be_2(SiO_4)$ [15191-85-2]

the surface of the bare metal, rendering the metal highly resistant to corrosion, to hot and cold water, and to oxidizing acids (Newland, 1984; Petzow *et al.*, 1985; WHO, 1990).

1.3 Use of the agents

Beryllium is primarily used in its metallic form, in alloys, or in beryllium oxide ceramics. Its physical and mechanical properties make it useful for many applications across a range of industries. These properties include: outstanding strength (when alloyed), high melting-point,

high specific heat, excellent thermal properties, electrical conductivity, reflectivity, low neutron absorption, and high neutron-scattering cross-sections, and transparency to X-rays (WHO, 1990; USGS, 2007).

Industries using beryllium and beryllium products include: aerospace (e.g. altimeters, braking systems, engines, and precision tools), automotive (e.g. air-bag sensors, anti-lock brake systems, steering wheel connecting springs), biomedical (e.g. dental crowns, medical laser components, X-ray tube windows), defence (e.g. heat shields, missile guidance systems, nuclear reactor components), energy and electrical (e.g. heat exchanger tubes, microwave devices, relays and switches), fire prevention (e.g. non-sparking tools, sprinkler system springs), consumer products (e.g. camera shutters, computer disk drives, pen clips), manufacturing (e.g. plastic injection moulds), sporting goods (e.g. golf clubs, fishing rods, naturally occurring and man-made gemstones), scrap recovery and recycling, and telecommunications (e.g. mobile telephone components, electronic and electrical connectors, undersea repeater housings) (Kreiss *et al.*, 2007).

1.3.1 Beryllium metal

Some typical applications of beryllium metal include: aerospace technology (structural material, inertia guidance systems, additives in solid propellant rocket fuels, aircraft brakes, mirror components of satellite optical systems, gyroscopes), nuclear technology (moderator and reflector of neutrons in nuclear reactors, neutron source when bombarded with α particles), X-ray and radiation technology (special windows for X-ray tubes), computer technology and alloys (e.g. beryllium–copper alloys; hardening of copper, and developmental brass alloys) (WHO, 1990; Petzow *et al.*, 2007).

1.3.2 Beryllium-containing alloys

Approximately 75% of manufactured beryllium is used in alloys, 95% of which is copper alloy (Jakubowski & Palczynski, 2007). Because of the properties it confers on other metals (i.e. low density combined with strength, high melting-point, resistance to oxidation, and a high modulus of elasticity), beryllium alloys are light-weight materials that can withstand high acceleration and centrifugal forces (WHO, 1990). Beryllium–copper alloys are commonly used in the electronics (e.g. switch and relay blades, electronic connector contacts, control bearings, magnetic sensing device housings, and resistance welding systems), automotive (e.g. air-bag sensors), military (e.g. electro-targeting and infrared countermeasure devices, missile systems, advanced surveillance satellites, and radar systems), and aerospace industries (e.g. landing gear bearings, weather satellites). Other applications include computers, oil exploration equipment, medical appliances, sporting equipment (e.g. golf clubs), and non-sparking tools (e.g. in petroleum refineries) (WHO, 1990; Kaczynski, 2004; Jakubowski & Palczynski, 2007).

1.3.3 Beryllium oxide

The ceramic properties of sintered beryllium oxide make it suitable for the production or protection of materials to be used at high temperatures in corrosive environments. It is used in lasers and electronics (e.g. transistor mountings, semiconductor packages, microelectronic substrates, microwave devices, high-powered laser tubes), in aerospace and military applications (e.g. gyroscopes and armour), refractories (e.g. thermocouple sheaths and crucibles), nuclear technology (reactor fuels and moderators), and medical/dental applications (e.g. ceramic crowns). It is also used as an additive (to glass, ceramics, and plastics) in the preparation of beryllium compounds, and as a catalyst for organic reactions (WHO, 1990; Taylor *et al.*, 2003).

1.3.4 Other beryllium compounds

Other important beryllium compounds include the beryllium halides (beryllium chloride and beryllium fluoride), beryllium hydroxide, and beryllium sulfate. Beryllium chloride has been used as a raw material in the electrolytic production of beryllium, and as the starting material for the synthesis of organo-beryllium compounds (O'Neil, 2006; Petzow *et al.*, 2007). Beryllium fluoride is used as an intermediate in the preparation of beryllium and beryllium alloys. It is used in nuclear reactors and glass manufacture, and as an additive to welding and soldering fluxes (O'Neil, 2006; Petzow *et al.*, 2007). Beryllium hydroxide is used as an intermediate in the manufacture of beryllium and beryllium oxide (O'Neil, 2006). Beryllium sulfate tetrahydrate is used as an intermediate in the production of beryllium oxide powder for ceramics (Kaczynski, 2004).

1.4 Environmental occurrence

Beryllium occurs naturally in the earth's crust, and is released in the environment as a result of both natural and anthropogenic activities. The environmental occurrence of beryllium has been reviewed extensively (WHO, 1990; ATSDR, 2002; Taylor *et al.*, 2003).

1.4.1 Natural occurrence

The 44th most abundant element in the earth's crust, beryllium occurs in rocks and minerals (mica schist, granite, pegmatite, and argillite), although the most highly enriched beryllium deposits are found in granitic pegmatites, in which independent beryllium minerals crystallize. Some 50 beryllium-containing minerals have been identified. Only ores containing beryl ($3BeO.Al_2O_3.6SiO_2$) and bertrandite ($4BeO.2SiO_2.H_2O$) have achieved economic significance. The average terrestrial abundance of beryllium is 2–5.0 mg/kg. (IARC, 1993; Jakubowski & Palczynski, 2007; USGS, 2007).

1.4.2 Air

Beryllium particulates are released in the atmosphere from both natural and anthropogenic sources. Windblown dust is the most important natural source of atmospheric beryllium (approximately 95%), with volcanic activity accounting for the remainder. The major anthropogenic source of atmospheric beryllium is the combustion of coal and fuel oil. Other sources include: municipal waste incineration, beryllium alloy and chemical use (includes ore processing, production, use and recycling), and the burning of solid rocket fuel (WHO, 2001; ATSDR, 2002). Ambient concentrations of atmospheric beryllium are generally low. Based on measurements at 100 locations, an average daily concentration of less than 0.5 ng/m^3 was reported in the United States of America (Jakubowski & Palczynski, 2007). Atmospheric concentrations of beryllium in the vicinity of beryllium-processing plants are often higher than those measured elsewhere (IARC, 1993).

1.4.3 Water

Beryllium is released in the aquatic environment from both natural and anthropogenic sources. Weathering of beryllium-containing rocks and soils is the primary source of release, although leaching of coal piles may also contribute to beryllium entering surface water. Anthropogenic sources include industrial waste water effluents (e.g. from electric utility industries). The deposition of atmospheric fall-out (of anthropogenic and natural sources) is also a source of beryllium in surface waters. However, the relative importance of this contribution to aquatic concentrations of beryllium is difficult to assess (ATSDR, 2002).

Beryllium concentrations in surface waters are usually in the range of 0.01–0.1 µg/L (WHO, 1990). The concentration of beryllium in deep ocean waters tend to be fairly uniform worldwide,

and are estimated to be approximately three orders of magnitude lower than that of surface river water (Jakubowski & Palczynski, 2007). Beryllium concentrations in drinking-water are on average 0.19 µg/L, with a range of 0.01–1.22 µg/L (Kolanz, 2001).

1.5 Human exposure

1.5.1 Exposure of the general population

The primary route of beryllium exposure for the general population is via the ingestion of contaminated food or water. The daily intake of beryllium by non-occupationally exposed persons in the USA from drinking-water is estimated to be 1 µg per day (assuming an average concentration of 0.5 µg/L, and a drinking-water consumption rate of 2 L/day). In the 1980s, the Environmental Protection Agency in the USA estimated the daily intake of beryllium in food to be approximately 0.12 µg per day (based on an arbitrary value of 0.1 ng beryllium per gram of food, and an assumption that a normal adult consumes 1200 g of food per day). Other studies have estimated the daily intake of beryllium in food to be in the range of 5–100 µg per day (ATSDR, 2002).

The inhalation of beryllium via ambient air or smoking is considered to be a minor exposure route for the general population. Assuming an average airborne concentration of less than 0.03 ng/ m^3 beryllium per day, and a breathing rate of 20 m^3 of air per day, the estimated daily intake for an adult in the USA is approximately 0.6 ng of beryllium, or less, per day. This estimated intake is likely to be higher for for persons living near point sources of beryllium emission (ATSDR, 2002).

1.5.2 Occupational exposure

The occupational environment is the predominant source of beryllium exposure for humans. Inhalation of beryllium dust and dermal contact with beryllium-containing products are the main routes of occupational exposure, although there may be the potential for in-home exposure if contaminated work garments are worn at home (ATSDR, 2002; NTP, 2004). Industries using or producing beryllium include: aerospace; automotive; biomedical; defence; energy and electrical; fire prevention; instruments, equipment and objects; manufacturing; sporting goods and jewellery; scrap recovery and recycling; and telecommunications (Kreiss *et al.*, 2007).

Based on data obtained from the primary beryllium industry and government agencies, Henneberger *et al.* (2004) estimated that 134000 workers were potentially exposed to beryllium in the USA (1500 in the primary beryllium industry, 26500 in the Department of Energy or Department of Defence, and between 26400 and 106000 in the private sector, outside of the primary industry). This figure may be an underestimate because of the limited data on potential beryllium exposures in military and nuclear weapons workplaces, and in many others where beryllium is a minor or unsuspected component (e.g. aluminium smelting, scrap recovery, and electronics recycling). The number of workers in the USA ever exposed to beryllium is likely to be far higher than 134000, as it does not include approximately 250000 construction workers that are employed at nuclear weapons reclamation sites alone (Kreiss *et al.*, 2007).

Estimates of the number of workers potentially exposed to beryllium and beryllium compounds have been developed by CAREX in Europe. Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX (CARcinogen EXposure) database estimates that 66069 workers were exposed to beryllium and beryllium compounds in the European Union, with over 80% of workers employed in the manufacture of machinery, except electrical (n = 38543); manufacture of fabricated metal products except machinery and equipment (n = 5434); manufacture of electrical machinery,

apparatus and appliances (n = 4174); manufacture of professional, scientific, measuring and controlling equipment not elsewhere classified (n = 3708); and manufacture of transport equipment (n = 3328). CAREX Canada estimates that 4000 Canadians (86% male) are exposed to beryllium in their workplaces (CAREX Canada, 2011). These industries include: building equipment contractors, medical equipment and supplies manufacturing, residential building construction, motor vehicle parts manufacture, automotive repair and maintenance, non-residential building construction, commercial/industrial machinery repair and maintenance, architectural and structural metals manufacturing.

Data on early occupational exposures to beryllium were summarized in the previous *IARC Monograph* (IARC, 1993), and data from studies on beryllium exposure published since are summarized below.

(a) Processing and manufacturing

Sanderson *et al.* (2001a) investigated historical beryllium exposures in a beryllium-manufacturing plant in the USA during 1935–92 for the purpose of reconstructing exposures for an epidemiological study. Daily weighted average (DWA) exposure estimates ranged from 1.7–767 μg/m^3 for 1935–60; 1.0–69.9 μg/m^3 for 1961–70; 0.1–3.1 μg/m^3 for 1971–80; and 0.03–1.4 μg/m^3 for 1981–92 (range of geometric means).

Seiler *et al.* (1996a, b) investigated historical beryllium exposure data (n = 643) collected in five beryllium-processing facilities in the USA during 1950–75. Descriptive data for representative job titles in November 1974 indicated that DWA beryllium exposures ranged from a minimum of 0.3 μg/m^3 for a ceramics machine operator to a maximum of 111.4 μg/m^3 for a vacuum cast furnace operator. Approximately 73% of the maximum breathing zone DWA exposures exceeded the 2 μg/m^3 standard; only 18% of the general air DWA beryllium exposures exceeded the standard.

Deubner *et al.* (2001a) analysed 34307 airborne beryllium measurements (general air, breathing zone, and personal lapel) collected during 1970–99 at a beryllium mining and extraction facility in Delta, UT, USA, and compared them to a mixed beryllium products facility and a beryllium ceramics facility located in Elmore, OH and Tucson, AZ, respectively. DWAs (n = 1519) were calculated to estimate task-specific, time-weighted average (TWA) exposures for workers at the Delta facility. The general area and breathing zone sampling data indicated that average annual beryllium concentrations at the Delta plant declined over the study period. The range of annual median general area sample concentrations at the mining and milling plant was comparable to that at the beryllium ceramics facility (0.1–0.6 μg/m^3 versus 0.1–0.4 μg/m^3, respectively). These data were lower than those observed at the mixed beryllium products facility (range of annual median general area sample concentrations, 0.1–1.0 μg/m^3). At the mining and milling facility, the highest exposures were observed in jobs involving beryllium hydrolysis and wet-grinding activities. This observation was independent of the exposure assessment method used.

Kreiss *et al.* (1997) analysed 106218 airborne beryllium measurements collected during 1984–93 at a beryllium-manufacturing plant producing pure metal, oxide, alloys, and ceramics. Of these, 90232 were area samples (30-minute samples: n = 30872; full-shift, continuous samples: n = 59360), and 15986 were personal samples (1–15 minute breathing zone samples: n = 15787; full-shift personal lapel samples: n = 179). Using these data, DWA exposures were calculated for most jobs. Median area concentrations were 0.6 μg/m^3 and 0.4 μg/m^3 for full-shift and short-term samples, respectively. Median personal concentrations were 1.4 μg/m^3 and 1.0 μg/m^3 for short-term and full-shift samples, respectively. The highest median area concentrations were observed in the alloy arc furnace

and alloy melting-casting areas, and the highest median breathing zone concentrations were observed in the beryllium powder and laundry areas.

Kent *et al.* (2001) collected full-shift particle-size-specific personal samples (n = 53) and area samples (n = 55) in five furnace areas at a beryllium-manufacturing facility. Personal samples were collected with Anderson impactors and general area samples were collected with micro-orifice uniform deposit impactors (MOUDIs). The median total mass concentration of beryllium particles (in μg/m^3) was reported by work process area and particle size. Median personal aerosol concentrations ranged from 0.8–5.6 μg/m^3 for total particle mass, and 0.05–0.4 μg/m^3 for alveolar-deposited particle mass. Median area concentrations ranged from 0.1–0.3 μg/m^3 for total particle mass, and 0.02–0.06 μg/m^3 for alveolar-deposited particle mass.

(b) Beryllium oxide ceramics

As part of a study to examine the relationship between sensitization and beryllium exposure in a beryllium ceramics plant in the USA, Kreiss *et al.* (1996) reviewed all general area (n = 5664) and personal breathing zone (n = 4208) samples collected during 1981–92. Of the area samples collected, 14% (n = 774) were full-shift samples collected from 1983 onwards; of the personal breathing zone samples, 1.7% (n = 75) were full-shift samples collected from 1991 onwards. Using average general area, full-shift area and breathing zone measurements, DWA exposures for most occupations were calculated. Of the full-shift area samples, 76% were reported to be at or below the detection limit of 0.1 μg/m^3. The median general area concentration was at or below the detection limit, with measured concentrations ranging as high as 488.7 μg/m^3. Median personal breathing zone concentrations were 0.3 μg/m^3 (maximum, 1931 μg/m^3) and 0.20 μg/m^3 (range, 0.1–1.8 μg/m^3) for the short-term and full-shift samples, respectively. Machinists were observed to have the highest exposures, with breathing zone concentrations of 63.7 μg/m^3, and a median DWA exposure of 0.9 μg/m^3.

Henneberger *et al.* (2001) conducted a follow-up to the Kreiss *et al.* (1996) study, screening workers at a US beryllium ceramics plant to determine whether the plant-wide prevalence of beryllium sensitization and disease had declined in the 6-year interval since first screening, and to explore exposure–response relationships. Historical airborne beryllium measurements (task- and time-specific) were combined with individual work histories to compute worker-specific beryllium exposures (mean, cumulative, and peak). A total of 18903 beryllium measurements were collected during 1981–98, of which 43% were short-term (1–15 minute), task-specific personal breathing zone samples, and 57% were short-term (30 minute) general area samples. Mean calculated exposures for all workers ranged from 0.05 μg/m^3 (i.e. less than the limit of detection) to 4.4 μg/m^3. When duration of employment was taken into account, short-term workers (i.e. those hired since the previous survey) had lower mean (median value: 0.28 μg/m^3 versus 0.39 μg/m^3) and peak concentrations (median value: 6.1 μg/m^3 versus 14.9 μg/m^3) than long-term workers.

Cummings *et al.* (2007) conducted a follow-up study in the same beryllium oxide ceramics manufacturing facility considered by Henneberger *et al.* (2001) to assess the effectiveness of an enhanced preventive programme to reduce beryllium sensitization. Sensitization for newly hired workers was compared with that for workers hired from 1993–98, and tested in the 1998 survey. Full-shift personal exposure data collected by the facility from 1994–2003 (n = 1203 measurements) was grouped into two time periods (1994–99 and 2000–03), and three work categories (production, production support, and administration). For the period 1994–99, median beryllium levels were 0.20 μg/m^3, 0.10 μg/m^3, and

less than the limit of detection in production, production support and administration, respectively (n = 412, full-shift personal lapel samples). For the later period, median beryllium levels were 0.18 μg/m^3, 0.04 μg/m^3, and 0.02 μg/m^3 in production, production support, and administration, respectively (n = 791, full-shift personal lapel samples).

(c) Machining and use

Martyny *et al.* (2000) conducted particle-size selective sampling on five mechanical processes (milling, deburring, lapping, lathe operations, and grinding) to examine the particle size distribution of beryllium machining exposures. Two sets of stationary samples were collected using Lovelace Multijet Cascade Impactors mounted to the machines at 'point of operation' and at 'nearest worker location', two sets of personal samples were collected in the breathing zone of workers operating the machines (one personal pump-powered lapel sampler, one personal cascade impactor), as well as ambient air samples from four fixed locations in the facility. In total, 336 measurements were collected (79 personal pump samples, 87 personal impactor samples, 71 nearest worker location samples, 87 point of operation samples, and 12 ambient air samples. Of these, 243 were samples of the five target processes (64 personal pump samples, 59 personal impactor samples, 64 nearest worker location samples, and 56 point of operation samples). For the stationary area samples, median TWA concentrations were in the range of 0.20 μg/m^3 for the 'nearest worker location' samples to 0.60 μg/m^3 for the 'point of operation' samples. For the personal breathing zone samples (collected by the personal impactors), median TWA concentrations were in the range of 0.13 μg/m^3 for lapping processes to 0.74 μg/m^3 for deburring operations. The range of 48-hour median ambient concentration was 0.02–0.07 μg/m^3.

To evaluate the effectiveness of a beryllium exposure control programme at an atomic weapons facility in Wales, United Kingdom, Johnson *et al.* (2001) analysed 585438 air monitoring records (367757 area samples collected at 101 locations, and 217681 personal lapel samples collected from 194 workers during 1981–97). Across all departments, the range of annual personal concentrations was 0.11–0.72 μg/m^3 (mean) and 0.08–0.28 μg/m^3 (median). The highest levels of exposure were observed in foundry workers, with a mean exposure level of 0.87 μg/m^3 and a median exposure level of 0.22 μg/m^3 (over all years). For the area samples, mean annual concentrations ranged from a high of 0.32 μg/m^3 in 1985 to a low of 0.02 μg/m^3 in 1997.

(d) Alloy facilities

Schuler *et al.* (2005) analysed airborne beryllium measurements collected in 1969–2000 at a beryllium–copper alloy strip and wire finishing facility. Of the 5989 available measurements, 650 were personal samples, 4524 were general area samples, and 815 were short-duration, high-volume (SD-HV) breathing zone samples. Data were grouped and analysed on the basis of work category (production, production support, administration), and by process or job within each work category. For example, 'rod and wire' production is a subcategory of 'production'; jobs within 'rod and wire' production include: wire annealing and pickling, wire drawing, straightening, point and chamfer, rod and wire packing, die grinding, and, historically, wire rolling. Median plant-wide exposure levels were 0.02 μg/m^3 (personal), 0.09 μg/m^3 (general area), and 0.44 μg/m^3 (SD-HV breathing zone). Among work categories, the highest levels of beryllium exposure were found in 'rod and wire' production (median, 0.06 μg/m^3), with the most highly exposed process or job being 'wire annealing and pickling' (median, 0.12 μg/m^3).

In a study in a beryllium alloy facility, Day *et al.* (2007) measured levels of beryllium in workplace air (n = 10), on work surfaces (n = 252), on cotton gloves worn over nitrile gloves (n = 113),

and on necks and faces of workers (n = 109). In production, geometric mean levels of beryllium were 0.95 µg/100 cm^2 (work surfaces), 42.8 µg per sample (cotton gloves), 0.07 µg per sample (necks), and 0.07 µg per sample (faces). In production support, geometric mean levels of beryllium were 0.59 µg/100 cm^2 (work surfaces), 73.8 µg per sample (cotton gloves), 0.09 µg per sample (necks), and 0.12 µg per sample (faces). The lowest levels were measured in the administration section, with geometric mean levels of beryllium of 0.05 µg/100 cm^2 (work surfaces), 0.07 µg per sample (cotton gloves), 0.003 µg per sample (necks), and 0.003 µg per sample (faces). Strong correlations were observed between beryllium in air and on work surfaces (r = 0.79), and between beryllium on cotton gloves and on work surfaces (r = 0.86), necks (r = 0.87), and faces (r = 0.86).

Yoshida *et al.* (1997) studied airborne beryllium levels at two beryllium–copper alloy manufacturing factories in Japan during 1992–95. General area samples were collected in the beryllium–copper alloy process (n = 56) and the beryllium–copper metal mould manufacturing process (n = 41) of Factory A, and in the beryllium–copper cold rolling, drawing and heat-treatment process (n = 16) and beryllium–copper slitting treatment process (n = 8) of Factory B. In all years studied, the highest geometric mean beryllium levels were observed in the beryllium–copper alloy process of Factory A (range, 0.16–0.26 µg/m^3).

Stanton *et al.* (2006) studied beryllium exposures among workers at three beryllium–copper alloy distribution centres in the USA in 2000–01. For the period 1996–2004, company records of full-shift personal lapel breathing zone samples for airborne beryllium (n = 393) were examined. A total of 54% of all samples were at or below the limit of detection. The overall median beryllium concentration was 0.03 µg/m^3 (arithmetic mean, 0.05 µg/m^3). When examined by work category (production – bulk products, production – strip metal, production support, administration) and process or job within work category, concentration ranges were 0.01–0.07 µg/m^3 (median), and 0.02–0.07 µg/m^3 (geometric mean). The highest concentrations were measured in heat-treating (bulk products) and tensioning (strip metal) processes, with levels of 1.6 µg/m^3 and 1.4 µg/m^3, respectively.

(e) Nuclear facilities

Stange *et al.* (1996a) studied beryllium exposures in the Rocky Flats Nuclear Facility in the USA. Fixed airhead (i.e. area) samples (n = 102) and personal breathing zone samples (n = 102) were collected from the main beryllium production building. The mean beryllium concentration from the area samples was 0.16 µg/m^3, and from the personal samples, 1.04 µg/m^3. No correlation (r^2 = 0.029) was observed between fixed airhead and personal breathing zone beryllium samples.

Stefaniak *et al.* (2003a) investigated historical beryllium exposure conditions at the Los Alamos Nuclear Laboratory in the USA. A total of 4528 personal breathing zone and area samples were analysed. For all technical areas, the geometric mean concentration for the period 1949–89 was 0.04 µg/m^3. Average beryllium concentrations per decade were less than 1 µg/m^3, and annual geometric mean concentrations in the area that was the largest user of beryllium were generally below 0.1 µg/m^3.

(f) Other

Meeker *et al.* (2006) compared occupational exposures among painters using three alternative blasting abrasives (specular hematite, coal slag, steel grit) on a footbridge painting project during 2002–04 in New Jersey, USA. Over the 3-year project, personal breathing zone samples were collected outside the respirators of two or three abrasive blasters. The range of beryllium concentrations measured outside personal protective equipment (n = 18 samples) was 2.5–9.5 µg/m^3, with a geometric mean exposure

level of 5.0 μg/m^3. Beryllium was also measured in bulk paint chips collected from each bridge.

Bauxite, from which aluminium is derived, may contain beryllium in varying degrees. In 965 personal samples collected during 2000–05 in four aluminium smelters, beryllium concentrations varied in the range of 0.002–13.0 μg/m^3 (arithmetic and geometric means were 0.22 and 0.05 μg/m^3, respectively) (Taiwo *et al.*, 2008).

1.5.3 Dietary exposure

There is a lack of reliable data on the concentration of beryllium in food (WHO, 1990; ATSDR, 2002). Measured concentrations of beryllium have been reported for 38 foods, fruit and fruit juices from around the world (number of samples, 2243; 2209 foods + 34 fruit and juices). Concentrations in the foods have been reported in the range of < 0.1–2200 μg/kg fresh weight, with the highest concentrations measured in kidney beans, crisp bread, garden peas, parsley and pears (2200, 112, 109, 77, and 65 μg/kg fresh weight, respectively), and with a median concentration of 22.5 μg/kg fresh weight (kidney beans were excluded from this calculation). Concentrations in the fruits and juices ranged from not detected to 74.9 μg/L, with an average concentration of 13.0 μg/L (ATSDR, 2002). Beryllium has also been measured in rice, head lettuce, and potatoes at 80 μg/kg, 330 μg/kg, and 0.3 μg/kg, respectively (Kolanz, 2001).

1.5.4 Biomarkers of exposure

Several analytical methods are available and have adequate sensitivity for measuring beryllium in biological samples. These include gas chromatography-electron capture (GC-ECD), graphite furnace atomic absorption spectrometry (GF-AAS), inductively coupled plasma atomic emission spectrometry (ICP-AES), and inductively coupled plasma mass spectrometry (ICP-MS). Biological matrices in which these methods can measure beryllium include: blood, urine, faeces, fingernails, hair, and lung tissue. Urinary beryllium is an indicator of current exposure, but is of uncertain utility for quantitative exposure assessment. Beryllium levels in blood, serum or plasma are indicators of the intensity of current exposure (ATSDR, 2002; NTP, 2004; NRC 2007).

The average burden of beryllium in the general population is 0.20 mg/kg in the lung and is below 0.08 mg/kg in other organs (Kolanz, 2001).

The mean concentration of beryllium in urine measured in about 500 non-occupationally exposed individuals in the USA during the Third National Health and Nutrition Examination Survey (NHANES III) was 0.22 μg/g of creatinine (Paschal *et al.*, 1998). Other studies reported mean urinary beryllium concentrations in the range of < 0.03–0.4 μg/L for non-occupationally exposed individuals (Apostoli & Schaller, 2001).

2. Cancer in Humans

The previous *IARC Monograph* on beryllium and beryllium compounds was based largely on evidence of elevated lung cancer mortality among 689 individuals (predominantly workers) entered into the US Beryllium Case Registry (Steenland & Ward, 1991; Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-02-Table2.1.pdf), and in a cohort of 9225 workers employed at seven beryllium-processing plants in the USA (Ward *et al.*, 1992). The cohort study included two plants that had been previously studied (Mancuso, 1979, 1980; Wagoner *et al.*, 1980) and Infante *et al.* (1980) had reported earlier on mortality in the Beryllium Case Registry cohort.

2.1 Cohort studies and nested case–control studies

The body of evidence available for the current evaluation of the carcinogenicity of beryllium in humans includes the two previously evaluated cohort studies and a nested case–control study initially reported by Sanderson *et al.* (2001b), and reanalysed with adjustment for temporal confounders by Schubauer-Berigan *et al.* (2008).

The Beryllium Case Registry study included 689 individuals entered alive into the registry and followed for mortality through to 1988 (Steenland & Ward, 1991); 34% were from the fluorescent tube industry, and 36% were from basic manufacturing. There were 158 deaths from pneumoconiosis and other respiratory disease, the category that included beryllium disease (Standard Mortality Ratio [SMR], 34.2; 95%CI: 29.1–40.0). The overall SMR for lung cancer was 2.00 (95%CI: 1.33–2.89), based on 28 deaths. Among those with acute beryllium disease, there were 17 lung cancer deaths (SMR 2.32; 95%CI: 1.35–3.72), and among those with chronic beryllium disease, ten lung cancer deaths (SMR 1.57; 95%CI: 0.75–2.89).

The cohort study included workers at seven beryllium-processing plants in the USA involved in various phases of beryllium processing with exposure to many forms of beryllium and beryllium compounds (Ward *et al.*, 1992). The study found a significantly elevated SMR of 1.26 (95%CI: 1.12–1.42) for lung cancer in the cohort overall, with significant excesses observed for the two oldest plants located in Lorain, Ohio, and Reading, Pennsylvania.

The SMR for lung cancer at the Lorain plant was 1.69 (95%CI: 1.28–2.19), and at the Reading plant, 1.24 (95%CI: 1.03–1.48). The Lorain plant, in operation during 1935–48, is thought to have had very high beryllium exposures. The majority of workers (84.6%) were employed for less than 1 year. Ninety-eight of the 1192 individuals employed at the Lorain plant (8.2%) were identified in the Beryllium Case Registry as having beryllium disease; 91 were of the acute form which has only been associated with very high beryllium exposure, six individuals had chronic beryllium disease, and one was of unknown type. A total of 11 lung cancer deaths occurred among the 98 individuals with beryllium disease (SMR, 3.33; 95%CI: 1.66–5.95), and 46 lung cancer deaths occurred among the remaining 1094 Lorain workers (SMR, 1.51; 95%CI: 1.11–2.02). All but one of the 57 lung cancer deaths occurred in latency categories < 15 years; for 15–30 years' latency, the SMR was 2.09 [95%CI: 1.30–3.21]; and for over 30 years' latency, 1.66 [95%CI: 1.16–2.31].

The plant in Reading, Pennsylvania, in operation during 1935–2001, employed 3569 workers during 1940–69. Among those, 53.8% were employed for less than 1 year, and only 17.2% were employed for more than 10 years. When the SMRs for lung cancer at the Reading plant were analysed by latency and duration of exposure, the highest SMR was observed for the category with less than 1 year of employment and duration and more than 30 years' latency (SMR = 1.42; [95%CI: 1.01–1.93]). Further analyses by decade of hire revealed that 92/120 lung cancer deaths occurred among workers hired before 1950 (SMR, 1.26; [95%CI: 1.02–1.55]). None of the newer plants included in the study had a significantly elevated SMR for lung cancer. However, non-significantly elevated SMRs were observed for four out of five plants operating in the 1950s for workers hired during that decade. The results were adjusted for smoking based on comparing smoking histories of 1466 (15.9%) of cohort members surveyed in 1968 with a survey of the US population conducted in 1965, resulting in SMRs of 1.12, 1.49 and 1.09 for the total cohort, the Lorain plant, and the Reading plant, respectively. [The Working Group noted that it is unclear that adjustment for differences in smoking patterns between cohort members and the US population in the late 1960s would accurately reflect patterns

in the 1940s that would be most relevant to interpreting the lung cancer excess. It is possible that using data from the 1960s would overestimate the impact of smoking.] SMRs based on county referent rates were also presented and for the cohort as a whole, the SMR was slightly increased to 1.32, the SMR declined for the Lorain plant to 1.60, and increased for the Reading plant to 1.42.

Subsequent to the publication of the Ward *et al.* (1992) study, the Beryllium Industry Scientific Advisory Committee suggested that the excess of lung cancer observed at the Lorain plant might be attributable to exposure to sulfuric acid mist and fumes rather than exposure to beryllium (BISAC, 1997). A reanalysis of the cohort study used alternative referent rates (for cities in which the two oldest plants were located) to compute expected number of lung cancers, alternative smoking risk factor estimates to adjust for differences in smoking habits between the cohort and the US population, and an alternative methodology to calculate the SMR for all plants combined (Levy *et al.*, 2002). The net effect of the reanalysis was to reduce the magnitude and statistical significance of the SMRs in the Ward *et al.* (1992) study. [The Working Group noted that there are several potential methodological limitations of this reanalysis. For instance, the city referent rates used for the calculation were not published, whereas Ward *et al.* (1992) used only published rates.]

Sanderson *et al.* (2001b) conducted a nested case–control study of lung cancer within one of the beryllium processing plants studied by Ward *et al.* (1992). This plant was selected for study because it was one of the two older plants in which an elevated lung cancer SMR was observed, and because industrial hygiene measurement data were available from as early as 1947. Details of the job–exposure matrix are provided in Sanderson *et al.* (2001a). Mortality was followed-up through 1992, and 142 lung cancer cases were identified. Cases were age- and race-matched to five controls through incidence-density sampling (Sanderson *et al.*, 2001b). The main findings of the Sanderson *et al.* (2001b) study were positive associations with average and maximum exposure lagged 10 and 20 years. This association did not appear to be confounded by smoking in an analysis that excluded professional workers.

Following some letters and critiques of the Sanderson *et al.* (2001b) study (Deubner *et al.*, 2001b, 2007; Sanderson *et al.*, 2001c; Levy *et al.*, 2007), a reanalysis of the study was carried out that adjusted for year of birth and an alternative minimal exposure value (the lowest detectable exposure level divided by two) in continuous exposure–response analyses (Schubauer-Berigan *et al.*, 2008; see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-02-Table2.2.pdf). After controlling for year of birth, significantly elevated odds ratios for 10-year lagged average beryllium exposure were found in the middle two exposure quartiles. The choice of an alternative minimal exposure value decreased the trend statistic for cumulative exposure but increased it for average exposure. In the continuous analysis of average 10-year lag dose, the parameter estimates and *P*-values were highly significant with control for year of birth. [The Working Group noted that several methodological articles were published regarding the incidence-density sampling methods used in the nested case–control study (Deubner & Roth, 2009; Hein *et al.*, 2009; Langholz & Richardson, 2009; Wacholder, 2009). Three of these articles affirmed the methodology used to select controls in the study (Hein *et al.*, 2009; Langholz & Richardson, 2009; Wacholder, 2009). The Working Group noted that the issues raised in the Deubner & Roth (2009) commentary did not undermine confidence in the results of the Schubauer-Berigan *et al.* (2008) reanalysis.]

2.2 Synthesis

A large body of evidence was evaluated by the Working Group and, in conclusion, elevated lung cancer mortality was observed in a study of individuals with beryllium disease and in a cohort study of workers at seven beryllium-processing plants. The association of the elevated lung cancer risks with beryllium exposure is supported by a large number of lung cancer cases and stable rate ratios, a consistency in findings among plants, higher risks of lung cancer among workers hired before 1950 (when exposures were at their highest), a greater risk of lung cancer in the US Beryllium Case Registry cohort (especially among those highly exposed who were diagnosed with acute pneumonitis), and greatest risks for lung cancer in the plants with the highest risk for acute pneumonitis and other respiratory disease. In addition, the nested case–control studies found evidence for an exposure–response relationship that was strongest when using the 10-year lag average-exposure metric. All of the epidemiological studies involved potential exposure to metallic beryllium as well as other beryllium compounds, and were unable to discern the specific effects of beryllium metal or specific beryllium compounds.

3. Cancer in Experimental Animals

Beryllium compounds have been tested for carcinogenicity by inhalation in rats and mice, by intratracheal or intrabronchial administration in rats, by intravenous administration to rabbits, by intraperitoneally administration to mice, and by intramedullary bone administration in rabbits.

To date, by all routes of exposure and in all species tested, all beryllium compounds examined have been shown to be carcinogenic (IARC, 1993).

3.1 Inhalation exposure

3.1.1 Mouse

In p53 heterozygous mice, lung tumours occurred after a single series of three consecutive daily inhalation exposures to beryllium metal (Finch *et al.*, 1998a).

3.1.2 Rat

The first inhalation study published on beryllium was with beryllium sulfate in rats, which induced lung tumours and chronic lung disease (Schepers *et al.*, 1957). Inhalation of single doses of beryllium metal (Nickell-Brady *et al.*, 1994), and exposure to beryllium sulfate for 6 months (Schepers *et al.*, 1957) or 72 weeks (Reeves *et al.*, 1967) caused lung tumours in rats. Beryl ore dust induced lung tumours in rats (Wagner *et al.*, 1969).

3.1.3 Hamster

A study of inhalation of beryl ore for 17 months in hamsters resulted in excess atypical lung proliferative lesions, some of which described as tumours (Wagner *et al.*, 1969). It is noteworthy that similar doses caused tumours in rats (Wagner *et al.*, 1969).

See Table 3.1.

3.2 Intratracheal administration

3.2.1 Rat

A single intratracheal administration of beryllium metal, beryllium oxide, and beryllium hydroxide once per week for 15 weeks caused lung tumours in rats (Groth *et al.*, 1980). Beryllium oxide caused lung tumours in rats (Ishinishi *et al.*, 1980; Litvinov *et al.*, 1983).

See Table 3.2.

Table 3.1 Studies of cancer in experimental animals exposed to beryllium (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, p53 Heterozygous (M, F) 6–19 mo Finch *et al.* (1998a)	Beryllium metal Single exposure to 47 µg or 3×/d 63 µg 15/group/sex	Lung (tumours, both sexes combined): P53–controls 0/30, low dose 0/29, high dose 4/28 (14%) Wild-type–0/28	$P = 0.048$	
Rat, Wistar and Sherman (M, F) 18 mo (22 mo for controls) Schepers *et al.* (1957)	Beryllium sulfate tetrahydrate Inhalation 35.8 µg/m^3 5.5 d/wk during 180 d 84, 139 controls	Lung (tumours): 76 in 52 rats that survived after exposure period Controls–0/139	NR	Incomplete reporting of the study, total tumours not incidence reported, disease outbreak killed 58 rats during exposure and afterwards, data not divided up by strain or sex
Rat, SD CD rats (M, F) 72 wk Reeves *et al.* (1967)	Beryllium sulfate tetrahydrate Inhalation 34.25 µg/m^3 7 h/d, 5 d/wk, 150/group	Lung (pulmonary alveolar adenocarcinomas, multiple): 43/43 (100%) rats alive past 13 mo Controls–none	NR	Age at start, 6 wk Incomplete reporting of the study, respiratory infections, dead rats thrown out due to postmortem changes
Rat, Charles River CD (M) For each ore – up to 23 mo Wagner *et al.* (1969)	Beryl ore or bertrandite ore Inhalation 15mg/m^3, 6 h/d, 5 d/wk (210–620 µg/m^3 beryllium) 93, 33 controls	*Beryl* Lung: **12 mo** 5/11 (45%) squamous metaplasias or small epidermoid tumours **17 mo** 18/19 (95%) lung tumours (alveolar cell tumours–7 adenomas, 9 adenocarcinomas, 4 epidermoid tumours) *Bertrandite* None Controls, none	NR	High crystalline silica content of bertrandite ore Incomplete reporting of the study

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Hamster, Syrian golden (M) 17 mo Wagner *et al.* (1969)	Beryl ore or bertrandite ore Inhalation 15 mg/m^3, 6 h/d, 5 d/wk 48/group	*Both ores* **12 mo** Atypical lung proliferations **17 mo** More atypical lesions in beryl-exposed hamsters No definitive tumours	NR	Incomplete reporting of the study, lung lesions called adenomas in the figure only, but were probably adenomatous hyperplasias, and not tumours
Rats, F344 (M, F) 14 mo Nickell-Brady *et al.* (1994)	Beryllium metal Inhalation (nose-only) Single exposure 40, 110, 360 and 430 µg (cohort of Lovelace High dose study) 30/group/sex	Lung (tumours): 64% Controls, NR		Age at start, 12 wk No incidence data by group or sex

d, day or days; F, female; h, hour or hours; M, male; mo, month or months; NR, not reported; wk, week or weeks

Table 3.2 Studies of cancer in experimental animals exposed to beryllium (intratracheal or intrabronchial exposure)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar (F) 18 mo Groth *et al.* (1980)	Intratracheal single exposure to 0.5 or 2.5 mg beryllium metal or beryllium–aluminum alloy, beryllium–copper alloy, beryllium–copper–cobalt alloy, beryllium–nickel alloy 35/group	Lung (adenomas or carcinomas): Beryllium metal– 2/3 (67%) low dose, 6/6 (100%) high dose Passivated beryllium metal– 7/11 (64%) low dose, 4/4 (100%) high dose Alloy groups– all negative Controls, 0/21 after 19 mo Beryllium hydroxide– 13/25 (52%) adenoma or adenocarcinoma	$P < 0.008$	Age at start, 3 mo Low beryllium content of alloys Incidence of animals sacrificed at 19 mo reported
Rat, Wistar (F) 19 mo Groth *et al.* (1980)	Intratracheal 50 µg beryllium hydroxide initially followed by 25 µg 10 mo later 35/group	Lung (tumours): 13/25 (52%); Controls, 0/21	$P = 0.0021$	Incidence in rats surviving 16 mo or more
Rat, Wistar (M) Life span Ishinishi *et al.* (1980)	Intratracheal instillation 1 mg beryllium oxide once/wk for 15 wk 30; 16 controls	Lung (tumours): 6/30 (20%, 4 benign, 2 malignant) Controls, 0/16		Animals/group at start NR Untreated controls, 3/4 adenomas have histology indicative of malignancy
Rat, albino (NR) Life span Litvinov *et al.* (1983)	Intratracheal Single exposure beryllium oxide, low- and high-temp fired 0.036, 0.36, 3.6, 18 mg/kg 300 controls	Lung (tumours, malignant): High temp fired– 0/76, 0/84, 2/77 (3%), 2/103 (2%) Low temp fired– 3/69 (4%), 7/81 (9%), 18/79 (23%), 8/26 (31%) Controls, 0/104	NR	

d, day or days; F, female; h, hour or hours; M, male; mo, month or months; NR, not reported; wk, week or weeks

Table 3.3 Studies of cancer in experimental animals exposed to beryllium (intravenous exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse Strain, sex and duration, NR Cloudman *et al.* (1949)	Zinc beryllium silicate (0.264 mg Be); beryllium oxide (1.54 mg Be) 20–22 injections (twice weekly) Number at start, NR	"Some mice" developed malignant bone tumours		Animals/group at start NR Only zinc beryllium silicate induced osteosarcomas
Rabbit Strain, sex and duration, NR Barnes & Denz (1950)	Beryllium metal Total dose, 40mg 24 animals	Bone (sarcomas): 2 surviving rabbits		Toxicity in 19 rabbits during first wk and mo (liver necrosis)
Rabbit Strain and sex, NR > 7 mo Gardner & Heslington (1946)	Zinc beryllium silicate and beryllium oxide 20 doses, total dose–1 g of particles 7 animals	Osteosarcomas: *Zinc beryllium silicate–* 7/7 (100%) that lived past 7 mo *Beryllium oxide–* 1		
Rabbit Strain and sex, NR > 1 yr Cloudman *et al.* (1949)	Zinc beryllium silicate (17 mg Be) or beryllium oxide (390 mg Be) 20–22 injections (twice weekly)	Bone (tumours): *Zinc beryllium silicate–* 4/5 (80%)		Animals/group at start NR
Rabbit Strain, NR (M, F) > 30 wk Barnes & Denz (1950)	Zinc beryllium silicate or beryllium silicate 6–10 injections 67 animals	Bone (sarcomas): *Zinc beryllium silicate–* 7/21 (33%) past 30 wk		Poor survival
Rabbit Strain, NR (M, F) > 11.5 mo Dutra & Largent (1950)	Beryllium oxide or calcined phosphor with beryllium oxide, zinc oxide and silica 20–26 injections 360–700 mg beryllium in beryllium oxide 64–90 mg beryllium in phosphor group	Osteosarcomas: *Beryllium oxide–* 6/6 (100%) *Phosphor–* 2/3 (67%) Controls, 0/50		Animals/group at start NR
Rabbit Strain, NR (M, F) 14–28 mo Hoagland *et al.* (1950)	Beryllium phosphate Zinc beryllium silicate Beryllium oxide 1–4-d intervals, unknown time period Doses not clear 24 animals	Osteosarcomas: *Zinc beryllium silicate–* 7/8 (88%) *Beryllium oxide–* 1		Small group size, lack of controls Incomplete reporting

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rabbit Strain and sex, NR 18 mo Araki *et al.* (1954)	Beryllium phosphate 1 g Beryllium oxide 1 g Beryllium oxide + zinc oxide Single dose 35 animals	Osteosarcomas: *Beryllium phosphate–* 2/4 (50%) *Beryllium oxide+zinc oxide–* 9/31 (29%)		Weight ≈2.0 kg Small numbers of animals, no appropriate controls
Rabbit (M) Strain, NR Janes *et al.* (1954)	Zinc beryllium silicate (1 g beryllium silicate, 33.6 mg beryllium oxide) Twice/wk for 10 wk 10 animals	Osteosarcomas: 5		Age at start, 9–11 mo Small group size, lack of controls
Rabbit Strain and sex, NR 57 wk Kelly *et al.* (1961)	Zinc beryllium silicate Twice/wk for 10 wk 14 animals	Osteosarcomas: 10/14 (71%)		Small group size, lack of controls
Rabbit Strain and sex, NR 15–18 mo Komitowski (1967)	Beryllium oxide Single 1 g dose 20 animals	Osteosarcomas: 3/20 (15%)		Lack of appropriate control group
Rabbit Strain and sex, NR 25 wk Fodor (1977)	Beryllium oxide (1%) Once/wk for 25 wk 60 animals	Sarcomas: 21/29 (72%)		Age at start, 6 mo Incomplete reporting, lack of appropriate control group

d, day or days; F, female; M, male; mo, month or months; NR, not reported; wk, week or weeks

Table 3.4 Studies of cancer in experimental animals exposed to beryllium (other routes of exposure)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, A/J (M) 32 wk Ashby *et al.* (1990)	Intraperitoneal Beryllium sulfate tetrahydrate 0, 0.02, 0.05, 0.1 mg/mouse/injection 3×/wk for 8 wk 20/group	Incidence (% given only): 15, 17, 33, 38% Lung tumours/mouse: 0.15, 0.17, 0.39, 0.38	r = 5.9 and 4.6 for middle and high doses (χ^2)	Age at start, 5–6 wk Purity, 99% Middle and high doses, significant
Rabbit Strain and sex, NR 1–2 yr Yamaguchi (1963)	Injection into bone marrow Beryllium oxide 10 mg twice/wk 55 animals	Bone (tumours): 26		
Rabbit, mixed breeds (M, F) 15–20 mo Tapp (1966)	Intramedullary injection Beryllium silicate powder 20 mg 12 animals	Osteogenic sarcomas: 4/12 (33%)		Age at start, 6 wk
Rabbit, mixed breeds (M, F) 25 mo Tapp (1969)	Implants (periosteal) Zinc beryllium silicate, beryllium oxide, beryllium silicate 10 mg 18 animals	Osteogenic sarcomas: 4/18 (22%)		Age at start, 6 and 8 wk
Rabbit Strain and sex, NR 24 mo Komitowski (1974)	Intramedullary injection Beryllium oxide No dose given 20 animals	Osteogenic sarcomas: 5/20 (25%)		Incomplete reporting, lack of appropriate control group
Rabbit Strain and sex, NR 21 mo Matsuura (1974)	Intramedullary implants Beryllium carbonate, beryllium acetate, beryllium acetylacetonate, beryllium laurate, beryllium stearate 173, 18, 3, 3	Osteosarcomas: *Beryllium carbonate*– 30 *Beryllium acetylacetonate*– 1		Incomplete reporting, small numbers in most groups
Rabbit, Fauve de Bourgogne, sex (NR) > 4 mo Mazabraud (1975)	Intraosseous injection Zinc beryllium silicate 1 g/cm^3 65 animals	Osteogenic sarcomas: 45/65 (69%)		Age at start, 15–20 wk Incomplete reporting Lack of appropriate control group
Rabbit (M) 56 wk Hiruma (1991)	Implants into bone Beryllium oxide 300 (after fracture), 300, 50 mg 10/group	Osteosarcomas: 10/10 (100%) 7/10 (70%) 1/10 (10%)		

F, female; M, male; mo, month or months; NR, not reported; wk, week or weeks; yr, year or years

3.3 Intravenous administration

3.3.1 Mouse

A mouse study reported bone tumours after intravenous injection of zinc beryllium silicate (Cloudman *et al.*, 1949).

3.3.2 Rabbit

Multiple intravenous injections of beryllium metal (Barnes & Denz, 1950), beryllium oxide (Gardner & Heslington, 1946; Dutra & Largent, 1950; Araki *et al.*, 1954; Komitowski, 1967; Fodor, 1977), beryllium silicate, beryllium phosphate (Araki *et al.*, 1954), and zinc beryllium silicate (Gardner & Heslington, 1946; Cloudman *et al.*, 1949; Barnes & Denz, 1950; Hoagland *et al.*, 1950; Janes *et al.*, 1954; Kelly *et al.*, 1961) caused osteosarcomas in rabbits, which were reviewed by Groth (1980).

See Table 3.3.

[The Working Group noted that although many of these studies had defficiency in reporting methods, the rarity of the induced tumours was considered to be compelling enough to consider them as a group.]

3.4 Other routes of exposure

3.4.1 Mouse

Beryllium sulfate injected intraperitoneally caused an increased incidence and multiplicity of lung tumours in A/J mice (Ashby *et al.*, 1990).

3.4.2 Rabbit

Intramedullary bone administration of beryllium oxide (Yamaguchi, 1963; Komitowski, 1974; Hiruma, 1991), beryllium silicate (Tapp, 1966), zinc beryllium silicate (Tapp, 1969; Mazabraud, 1975), beryllium carbonate (Matsuura, 1974), and beryllium acetylacetonate (Matsuura, 1974) caused osteosarcomas or other bone tumours in rabbits.

See Table 3.4.

3.5 Synthesis

Lung tumours were induced in rats by inhalation of beryllium sulfate, beryllium metal, and beryl ore dust. In mice, lung cancer occurred after inhalation of beryllium metal. In hamsters, inhalation of beryl ore induced adenomatous hyperplasia of the lung. Intratracheal instillation of beryllium metal, beryllium hydroxide, and beryllium oxide in rats induced lung tumours. Intraperitoneal injection of beryllium sulfate induced lung tumours in mice. Intravenous injection or intramedullary injection/implantation of various beryllium compounds induced osteosarcoma in various studies in rabbits, and in one study in mice.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

The bioavailability of beryllium particles as a function of size (geometric mean diameter), chemical composition, and specific surface area has been studied extensively. The agglomeration of beryllium particles does occur but the agglomerates dissociate again in fluid, with a corresponding decrease in particle mean diameter (Kent *et al.*, 2001; Stefaniak *et al.*, 2003b, 2004, 2007). Highly significant associations of chronic beryllium disease (CBD) and beryllium sensitization with particle-mass concentration for particles of less than 10 μm have been observed. The particle-mass concentration of alveolar-deposited particles (< 10 μm) correlates significantly with the occurrence of CBD. In a simulated phagolysosomal fluid, dissolution rate constants (k) for metallic beryllium particles and multiconstituent particles from arc-furnace processing of a beryllium–copper alloy were greater than those observed for beryllium oxide materials (Stefaniak *et al.*, 2006). Beryllium has

been detected in CBD-associated granulomas of beryllium-exposed workers by secondary ion mass-spectroscopy at an average of 9 years post exposure (Sawyer *et al.*, 2005a). These data indicate that beryllium is retained in granulomatous lesions for extended periods of time in exposed humans with CBD. Verma *et al.*, (2003) also reported elevated concentrations of beryllium in lung tissue from a person with CBD.

Acute inhalation dose–response studies in mice with a follow-up period of 350 days showed that high-dose exposures produced granulomatous beryllium lesions, which impeded the clearance of beryllium from the lungs (Finch *et al.*, 1998b).

Accidental exposure of 25 people to beryllium dust produced a mean serum concentration of 3.5 µ/L measured one day later, which decreased to a mean concentration of 2.4 µ/L after 6 days (Zorn *et al.*, 1986). These data indicate that beryllium from beryllium metal is biologically available from the lung. Exposure to beryllium metal (Williams, 1977) and beryllium alloys (Lieben *et al.*, 1964) have been reported to produce beryllium disease.

4.2 Genetic and related effects

4.2.1 Direct genotoxicity

A large number of mutagenicity studies for beryllium compounds have been published (for reviews see IARC, 1993; Gordon & Bowser, 2003). In general, results of these studies have been either negative or weakly positive, depending on the test system used.

Joseph *et al.* (2001) studied gene expression patterns in BALB/c-3T3 cells transformed with beryllium sulfate and reported a general upregulation of several cancer-related genes. Because no toxicity data were provided in these studies, the relevance of these findings to cancer cannot be interpreted. The same authors also reported the downregulation of several genes involved in DNA synthesis, repair and recombination in the tumour cells relative to controls.

Fahmy *et al.* (2008) studied the genotoxicity of beryllium chloride in mice exposed to oral doses of 93.75–750 mg/kg body weight for 3 weeks. Starting with the second lowest concentration (187.5 mg/kg bw; 1/8 of the LD_{50}), chromosomal aberrations (excluding gaps) and aneuploidy were observed both in bone-marrow cells and in spermatocytes, as a function of dose and time.

4.2.2 Indirect effects related to genotoxicity

(a) Oxidative stress

Palmer *et al.* (2008) demonstrated upregulation of the protein PD-1 (programmed death-1) in beryllium-specific CD4+ T-cells derived from broncho-alveolar lavages from beryllium-sensitized persons or CBD patients. Upregulation of PD-1 was closely correlated with the severity of T-cell alveolitis.

Subsequent studies by Sawyer *et al.* (2005b) in mouse macrophages demonstrated beryllium-induced formation of reactive oxygen species *in vitro*, with marked increases in apoptosis and activation of caspase 8. These effects were attenuated by the addition of the antioxidant manganese(III)*meso*-tetrakis(4-benzoic acid) porphyrin (MnTBAP).

The inflammatory processes associated with the development of acute or chronic beryllium disease could plausibly contribute to the development of lung cancer by elevating the rate of cell turnover, by enhancing oxidative stress, and by altering several signalling pathways involved in cell replication.

(b) Epigenetic mechanisms

Studies by Belinsky *et al.* (2002) in beryllium-induced rat lung tumours demonstrated hypermethylation of the *p16* and *estrogen-receptor-α* genes, and their attendant inactivation.

4.3 Synthesis

Several molecular mechanisms, possibly interrelated, operate in beryllium-induced carcinogenesis. Whereas mutagenicity tests with beryllium have shown only weakly positive or negative results, chromosomal aberrations and aneuploidy were observed *in vivo* in mice, at non-toxic concentrations. Like many other carcinogenic metals, beryllium is capable of producing oxidative stress, which can lead to cell injury in the form of DNA damage, activation of proto-oncogenes, and apoptotic mechanisms. In addition, the toxicity of beryllium in the lung may lead to cell killing and compensatory cell proliferation. Furthermore, the beryllium-induced chronic inflammatory response with attendant release of cytokines from beryllium-reactive CD4+ T-cells could also play a role in the development of a carcinogenic response in lung tissue.

In addition to beryllium-mediated generation of reactive oxygen species, inflammatory processes induced by beryllium may also cause an increase in reactive oxygen species, mediate cell turnover, and alter cell-signalling pathways. Furthermore, downregulation of genes involved in DNA synthesis, repair and recombination also occurs. Thus, the processes underlying beryllium-induced carcinogenesis are clearly complex, with several possible interactive mechanisms.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of beryllium and beryllium compounds. Beryllium and beryllium compounds cause cancer of the lung.

There is *sufficient evidence* in experimental animals for the carcinogenicity of beryllium and beryllium compounds.

Beryllium and beryllium compounds are *carcinogenic to humans (Group 1).*

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CADMIUM AND CADMIUM COMPOUNDS

Cadmium and cadmium compounds were considered by previous IARC Working Groups in 1972, 1975, 1987, and 1993 (IARC, 1973, 1976, 1987, 1993a). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms, trade names and molecular formulae for cadmium, cadmium–copper alloy, and some cadmium compounds are presented in Table 1.1. The cadmium compounds shown are those for which data on carcinogenicity or mutagenicity were available or which are commercially important compounds. It is not an exhaustive list, and does not necessarily include all of the most commercially important cadmium-containing substances.

1.2 Chemical and physical properties of the agents

Cadmium (atomic number, 48; relative atomic mass, 112.41) is a metal, which belongs to group IIB of the periodic table. The oxidation state of almost all cadmium compounds is +2, although a few compounds have been reported in which it is +1. Selected chemical and physical properties of cadmium compounds are presented in the previous *IARC Monograph* (IARC, 1993a).

1.3 Use of the agents

Cadmium metal has specific properties that make it suitable for a wide variety of industrial applications. These include: excellent corrosion resistance, low melting temperature, high ductility, high thermal and electrical conductivity (National Resources Canada, 2007). It is used and traded globally as a metal and as a component in six classes of products, where it imparts distinct performance advantages. According to the US Geological Survey, the principal uses of cadmium in 2007 were: nickel–cadmium (Ni–Cd) batteries, 83%; pigments, 8%; coatings and plating, 7%; stabilizers for plastics, 1.2%; and other (includes non-ferrous alloys, semiconductors and photovoltaic devices), 0.8% (USGS, 2008).

Cadmium is also present as an impurity in non-ferrous metals (zinc, lead, and copper), iron and steel, fossil fuels (coal, oil, gas, peat, and wood), cement, and phosphate fertilizers. In these products, the presence of cadmium generally does not affect performance; rather, it is regarded as an environmental concern (International Cadmium Association, 2011). Cadmium is also produced from recycled materials (such as Ni–Cd batteries and manufacturing scrap) and some

Table 1.1 Chemical names, synonyms (CAS names are in italics), and molecular formulae of cadmium and cadmium compounds

Chemical name	CAS Reg. No.[a]	Synonyms	Formula
Cadmium	7440-43-9	Cadmium metal	Cd
Cadmium acetate	543-90-8 (24 558-49-4; 29 398-76-3)	*Acetic acid, cadmium salt*; bis(acetoxy)-cadmium; cadmium (II) acetate; cadmium diacetate; cadmium ethanoate	$Cd(CH_3COO)_2$
Cadmium carbonate	513-78-0 [93820-02-1]	*Carbonic acid, cadmium salt*; cadmium carbonate ($CdCo_3$); cadmium monocarbonate	$CdCO_3$
Cadmium chloride	10 108-64-2	Cadmium dichloride; dichlorocadmium	$CdCl_2$
Cadmium hydroxide	21 041-95-2 (1 306-13-4; 13 589-17-8)	*Cadmium hydroxide ($Cd(OH)_2$)*; cadmium dihydroxide	$Cd(OH)_2$
Cadmium nitrate	10 325-94-7 (14 177-24-3)	*Nitric acid, cadmium salt*; cadmium dinitrate; cadmium (II) nitrate	$Cd(NO_3)_2$
Cadmium stearate	2223-93-0	Cadmium distearate; cadmium octadecanoate; cadmium(II) stearate; octadecanoic acid, cadmium salt; *stearic acid, cadmium salt*	$Cd(C_{36}H_{72}O_4)$
Cadmium sulfate	10 124-36-4 (62 642-07-3) [31119-53-6]	Cadmium monosulfate; cadmium sulfate; *sulfuric acid, cadmium salt (1:1)*	$CdSO_4$
Cadmium sulfide	1306-23-6 (106 496-20-2)	Cadmium monosulfide; cadmium orange; cadmium yellow	CdS
Cadmium oxide	1306-19-0	Cadmium monoxide	CdO
Cadmium–copper alloy[b]	37 364-06-0	*Copper base, Cu, Cd*	Cd.Cu
	12 685-29-9 (52 863-93-1)	*Cadmium nonbase, Cd, Cu*	
	132 295-56-8	*Copper alloy, base, Cu 99.75–100, Cd 0.05–0.15*; UNS C14300	
	132 295-57-9	*Copper alloy, base, Cu 99.60–100, Cd 0.1–0.3*; UNS C14310	

[a] Replaced CAS Registry numbers are shown in parentheses; alternative CAS Registry numbers are shown in brackets.
[b] Sample of cadmium–copper alloys registered with the Chemical Abstracts Service

residues (e.g. cadmium-containing dust from electric arc furnaces) or intermediate products. Recycling accounts for approximately 10–15% of the production of cadmium in developed countries (National Resources Canada, 2007).

The primary use of cadmium, in the form of cadmium hydroxide, is in electrodes for Ni–Cd batteries. Because of their performance characteristics (e.g. high cycle lives, excellent low- and high-temperature performance), Ni–Cd batteries are used extensively in the railroad and aircraft industry (for starting and emergency power), and in consumer products (e.g. cordless power tools, cellular telephones, camcorders, portable computers, portable household appliances and toys) (ATSDR, 2008; USGS, 2008).

Cadmium sulfide compounds (e.g. cadmium sulfide, cadmium sulfoselenide, and cadmium lithopone) are used as pigments in a wide variety of applications, including engineering plastics, glass, glazes, ceramics, rubber, enamels, artists colours, and fireworks. Ranging in colour from yellow to deep-red maroon, cadmium pigments have good covering power, and are highly resistant to a wide range of atmospheric and environmental conditions (e.g. the presence of hydrogen

sulfide or sulfur dioxide, light, high temperature and pressure) (Herron, 2001; ATSDR, 2008; International Cadmium Association, 2011).

Cadmium and cadmium alloys are used as engineered or electroplated coatings on iron, steel, aluminium, and other non-ferrous metals. They are particularly suitable for industrial applications requiring a high degree of safety or durability (e.g. aerospace industry, industrial fasteners, electrical parts, automotive systems, military equipment, and marine/offshore installations) because they demonstrate good corrosion resistance in alkaline or salt solutions, have a low coefficient of friction and good conductive properties, and are readily solderable (UNEP, 2008; International Cadmium Association, 2011).

Cadmium salts of organic acids (generally cadmium laurate or cadmium stearate, used in combination with barium sulfate) were widely used in the past as heat and light stabilizers for flexible polyvinyl chloride and other plastics (Herron, 2001; UNEP; 2008). Small quantities of cadmium are used in various alloys to improve their thermal and electrical conductivity, to increase the mechanical properties of the base alloy (e.g. strength, drawability, extrudability, hardness, wear resistance, tensile, and fatigue strength), or to lower the melting point. The metals most commonly alloyed with cadmium include copper, zinc, lead, tin, silver and other precious metals. Other minor uses of cadmium include cadmium telluride and cadmium sulfide in solar cells, and other semiconducting cadmium compounds in a variety of electronic applications (Morrow, 2001; UNEP, 2008; International Cadmium Association, 2011).

Traditionally, the most common end-use applications for cadmium were pigments, stabilizers, and coatings. However, in recent years, the use of cadmium for these purposes has declined, mainly due to concerns over the toxicity of cadmium, and the introduction of regulations, particularly in the European Union, restricting its use (National Resources Canada, 2007).

1.4 Environmental occurrence

Historical information on the occurrence of cadmium and cadmium compounds can be found in the previous *IARC Monograph* (IARC, 1993a).

Cadmium occurs naturally in the earth's crust and in ocean water. It is emitted to the environment as a result of both natural and anthropogenic activities. Natural sources of cadmium include volcanic activity, weathering of cadmium-containing rocks, sea spray, and mobilization of cadmium previously deposited in soils, sediments, landfills, etc. Anthropogenic sources of cadmium include the mining and smelting of zinc-bearing ores, the combustion of fossil fuels, waste incineration, and releases from tailings piles or municipal landfills (UNEP, 2008; ATSDR, 2008).

1.4.1 Natural occurrence

In the earth's crust, cadmium appears mainly in association with ores containing zinc, lead, and copper (in the form of complex oxides, sulfides, and carbonates). Elemental cadmium is a soft, silver-white metal, which is recovered as a by-product of zinc mining and refining. The average terrestrial abundance of cadmium is 0.1–0.2 mg/kg, although higher concentrations are found in zinc, lead, and copper ore deposits. Naturally occurring cadmium levels in ocean water range, on average, from < 5 to 110 ng/L. (National Resources Canada, 2007; ATSDR, 2008; UNEP, 2008)

1.4.2 Air

Particulate cadmium (as elemental cadmium and cadmium oxide, sulfide or chloride) is emitted to the atmosphere from both natural and anthropogenic sources. Weathering and erosion of cadmium-bearing rocks is the most important natural source of cadmium. Other natural sources include volcanoes, sea spray, and

forest fires. The principal anthropogenic sources are non-ferrous metal production and fossil fuel combustion, followed by ferrous metal production, waste incineration, and cement production (WHO, 2000; ATSDR, 2008; UNEP, 2008)

Cadmium does not break down in the environment. Atmospheric cadmium compounds are transported (sometimes for long distances) and deposited (onto surface soils and water) with minimal transformation in the atmosphere (ATSDR, 2008). There is uncertainty about the relative magnitude of natural emissions versus anthropogenic emissions. Total global anthropogenic emissions in the mid-1990s were estimated at approximately 3000 tonnes. During 1990–2003, anthropogenic emissions of cadmium reportedly decreased by about half in Europe, and by about two-thirds in Canada (UNEP, 2008).

Mean total cadmium concentrations in air vary according to proximity to industrial source, and to population density. Measurement data from northern Europe for the period 1980–88 were reported as being around 0.1 ng/m^3 in remote areas, 0.1–0.5 ng/m^3 in rural areas, 1–10 ng/m^3 in urban areas, and 1–20 ng/m^3 in industrial areas, with levels of up to 100 ng/m^3 being observed near emission sources (WHO, 2000). Similar variations were observed in the USA (UNEP, 2008).

1.4.3 Water

Cadmium enters the aquatic environment from numerous diffuse (e.g. agricultural and urban run-off, atmospheric fall-out) and point sources, both natural and anthropogenic. Weathering and erosion of cadmium-containing rocks result in the release of cadmium not only to the atmosphere, but also to the soil and the aquatic system (directly and through the deposition of airborne particles) (ATSDR, 2008; UNEP, 2008). Cadmium is released to the aquatic environment from a range of anthropogenic sources, including non-ferrous metal mining and smelting (from mine drainage water, waste water, tailing pond overflow, rainwater run-off from mine areas), plating operations, phosphate fertilizers, sewage-treatment plants, landfills, and hazardous waste sites (IARC, 1993a; ATSDR, 2008).

Weathering and erosion are estimated to contribute 15000 tonnes of cadmium annually to the global aquatic environment, while atmospheric fall-out (of anthropogenic and natural emissions) is estimated to contribute between 900 and 3600 tonnes (UNEP, 2008).

1.4.4 Soil and sediments

Natural and anthropogenic sources (e.g. mine/smelter wastes, commercial fertilizers derived from phosphate ores or sewage sludge, municipal waste landfills) contribute to the levels of cadmium found in soil and sediments. Wet or dry deposition of atmospheric cadmium on plants and soil can lead to cadmium entering the food-chain through foliar absorption or root uptake. The rate of cadmium transfer depends on a variety of factors, including deposition rates, type of soil and plant, the pH of the soil, humus content, availability of organic matter, treatment of the soil with fertilizers, meteorology, and the presence of other elements, such as zinc (WHO, 2000; UNEP, 2008). Reported sediment concentrations of cadmium range from 0.03–1 mg/kg in marine sediments to as high as 5 mg/kg in river and lake sediments (Nordic Council of Ministers, 2003). Relatively high concentrations of cadmium (> 1 mg/kg) have been measured in the soil near smelters and other industrialized areas (WHO, 2000).

1.5 Human exposure

1.5.1 Exposure of the general population

The non-smoking general population is exposed to cadmium primarily via ingestion of food and, to a lesser extent, via inhalation of

ambient air, ingestion of drinking-water, contaminated soil or dust. For the US population, the geometric mean daily intake of cadmium in food is estimated to be 18.9 µg/day. In most countries, the average daily intake of cadmium in food is in the range of 0.1–0.4 µg/kg body weight (CDC, 2005; ATSDR, 2008; UNEP, 2008; EFSA, 2009)

Because tobacco leaves naturally accumulate large amounts of cadmium (Morrow, 2001), cigarettes are a significant source of cadmium exposure for the smoking general population. It has been estimated that tobacco smokers are exposed to 1.7 µg cadmium per cigarette, and about 10% is inhaled when smoked (Morrow, 2001; NTP, 2005). Data on blood and urine levels of smokers are found in Section 1.6.

1.5.2 Occupational exposure

The main route of cadmium exposure in the occupational setting is via the respiratory tract, although there may be incidental ingestion of dust from contaminated hands, and food (ATSDR, 2008). Occupations in which the highest potential exposures occur include cadmium production and refining, Ni–Cd battery manufacture, cadmium pigment manufacture and formulation, cadmium alloy production, mechanical plating, zinc smelting, brazing with a silver–cadmium–silver alloy solder, and polyvinylchloride compounding. Although levels vary widely among the different industries, occupational exposures generally have decreased since the 1970s. For more details on historical occupational exposures to cadmium, see the previous *IARC Monograph* (IARC, 1993a).

Estimates of the number of workers potentially exposed to cadmium and cadmium compounds have been developed by CAREX in Europe. Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX (CARcinogen EXposure) database estimates that 207350 workers were exposed to cadmium and cadmium compounds in the European Union, with over 50% of workers employed in the construction (n = 32113), manufacture of fabricated metal products (n = 23541), non-ferrous base metal industries (n = 22290), manufacture of plastic products not elsewhere classified (n = 16493), personal and household services (n = 15004), and manufacture of machinery except electrical (n = 13266).

CAREX Canada estimates that 35000 Canadians (80% males) are exposed to cadmium in their workplaces (CAREX Canada, 2011). The largest exposed group are workers in polyvinyl chloride plastic product manufacturing (n = 12000), who are exposed to cadmium-bearing stabilizers. Other industries in which exposure occurs include: foundries, commercial and industrial machinery manufacturing, motor vehicle parts manufacture, architectural and structural metal manufacturing, non-ferrous metal (except aluminium) production and processing, metalworking machinery manufacturing, iron and steel mills and ferro-alloy manufacturing, alumina and aluminium production and processing, and other electrical equipment and component manufacture.

Data from studies published since the previous *IARC Monograph* on exposure to cadmium and cadmium compounds in different occupational situations are summarized below.

(a) Battery manufacture

Zhang *et al.* (2002) investigated the renal damage of cadmium-exposed workers in an Ni–Cd battery factory in the People's Republic of China between April and May 1998. Based on area sampling measurements collected during 1986–92, the geometric mean concentration of cadmium oxide dust was 2.17 mg/m^3, with a range of 0.1–32.8 mg/m^3. The overall geometric mean urinary cadmium concentration for the 214 workers was 12.8 µg/g creatinine (range of geometric means, 4.0–21.4 µg/g creatinine), and the overall geometric mean blood cadmium

concentration was 9.5 µg/L (range of geometric means, 3.8–17.4 µg/L).

Cumulative exposure to cadmium hydroxide in Ni–Cd battery workers in the United Kingdom (n = 926 male workers) was investigated during 1947–2000. Mean cadmium concentrations in air from personal samples were highest in the 1969–73 period (range, 0.88–3.99 mg/m^3), and were lowest in the 1989–92 period (range, 0.024–0.12 mg/m^3). Mean cadmium concentrations in air from static area samples were highest in the 1954–63 period (range, 0.35–1.29 mg/m^3), and were lowest in the 1989–92 period (range, 0.002–0.03 mg/m^3) (Sorahan & Esmen, 2004).

(b) Cadmium recovery

Occupational exposure to cadmium compounds (oxide, sulfide, and sulfate) was investigated in male production workers (n = 571) from a cadmium recovery facility in the USA during 1940–82. Estimates of airborne cadmium exposures in the production departments ranged from 0.2 (in the tankhouse) to 1.5 mg/m^3 (in the mixing, calcine and retort departments) before 1950, and from 0.02 (in the tankhouse) to 0.6 mg/m^3 (in the sampling and roaster departments) for the 1965–76 time period (Sorahan & Lancashire, 1997).

(c) Cadmium alloy production

Occupational exposure to cadmium oxide fumes was investigated in 347 copper–cadmium alloy workers, 624 workers employed in the vicinity of copper–cadmium alloy work, and 521 iron and brass foundry workers in England and Wales during 1922–80. Based on a review of 933 measurements of airborne cadmium made during 1951–83 (697 area samples, 236 personal samples), cumulative cadmium exposures were estimated to be 600 µg/m^3 for the 1926–30 time period, dropping to an estimated 56 µg/m^3 by the 1980s (Sorahan *et al.*, 1995).

(d) Smelting

Occupational exposure to cadmium was investigated in 1462 male employees in a tin smelter in the United Kingdom during 1972–91. Annual average exposures in the principal process areas were reported. Average air levels were negligible in the dry-refining and electro-refining areas, low in the raw materials handling and roasters and ball mill areas (range of averages, 0.005–0.008 mg/m^3), and moderate in the sintering and blast furnace areas (range of averages, 0.04–0.08 mg/m^3) (Jones *et al.*, 2007).

(e) Vehicle manufacture

Wang *et al.* (2006) evaluated the exposure to metals of 82 welders and 51 operators in two vehicle-manufacturing plants in China. The geometric mean concentration of cadmium in the blood of welders was 3.54 µg/L (range, 0.2–12.5 µg/L), and was significantly higher than the control group concentration of 0.79 µg/L (range, 0.1–4.8 µg/L).

(f) Population-based surveys

Yassin & Martonik (2004) calculated the prevalence and mean urinary cadmium levels for all US workers, based on data collected from 11228 US workers aged 18–64 years who participated in the Third National Health and Nutrition Examination Survey (NHANES III, 1988–94). For all workers, urinary cadmium levels were in the range of 0.01–15.57 µg/L, with a geometric mean of 0.30 µg/L (0.28µg/g creatinine). The prevalence of elevated urinary cadmium levels was reported on the basis of the following ranges: ≥ 15 µg/L, ≥ 10 µg/L, ≥ 5 µg/L, and ≥ 3 µg/L. For all US workers aged 18–64 years, the prevalence of urinary cadmium levels ≥ 5 µg/L was 0.42% (n = 551000), for levels ≥ 10 µg/L, 0.06% (n = 78 471), and for levels ≥ 15 µg/L, 0.0028% (n = 3907). The proportion of workers with elevated urinary cadmium varied by occupation and industry. Within industry, urinary

cadmium levels ≥ 10 µg/L were twice as prevalent among workers in the metal industry compared to workers in the manufacturing industry (0.45% versus 0.26%). Within occupation, urinary cadmium levels ≥ 5 µg/L were 12 times as prevalent among vehicle mechanics than in transportation workers (1.71% versus 0.14%), and five times as prevalent in construction workers than in agriculture workers (0.73% versus 0.14%).

1.5.3 Dietary exposure

Low levels of cadmium have been measured in most foodstuffs (average concentrations are less than 0.02 µg/g). Factors influencing cadmium levels in food include: food type (e.g. seafood or leafy vegetables versus meat or dairy), growing conditions (e.g. soil type, water), agricultural and cultivation practices, meteorological conditions (i.e. rate of atmospheric deposition), and anthropogenic contamination of soil or aquatic system (UNEP, 2008; EFSA, 2009; WHO, 2011). Highly contaminated areas have higher cadmium concentrations in locally produced food, and the use of cadmium-containing fertilizers in agriculture increase cadmium concentrations in the crops, and derived products.

High concentrations of cadmium are found in leafy vegetables (e.g. lettuce, spinach), starchy roots (e.g. potatoes), cereals and grains, nuts and pulses (e.g. peanuts, soybeans, sunflower seeds). Lower concentrations of cadmium are found in meat and fish, with the exception of certain shellfish (e.g. oysters), and certain organ meats (e.g. kidney and liver), which concentrate cadmium. Weekly dietary intake estimates in the EU are in the range of 1.9–3.0 µg/kg body weight (mean, 2.3 µg/kg body weight) for non-vegetarians. Vegetarians, regular consumers of bivalve mollusks, and wild mushrooms are, respectively, estimated to have weekly dietary cadmium exposures of 5.4 µg, 4.6 µg, and 4.3 µg (per kg of body weight). On a body weight basis, estimated cadmium intakes are generally higher for infants and children than for adults (UNEP, 2008; EFSA, 2009).

1.5.4 Biomarkers of exposure

Several analytical procedures are available for measuring cadmium concentrations in biological samples. These include: atomic absorption spectroscopy (AAS), electrothermal atomic absorption spectroscopy (ET-AAS), flame atomic absorption, graphite furnace atomic absorption, inductively coupled plasma atomic emission spectroscopy (ICP-AES), inductively coupled plasma mass spectrometry (ICP-MS), neutron activation analysis, potentiometric stripping analysis, radiochemical neutron activation analysis, X-ray fluorescence, and treatment with methyl isobutyl ketone, ammonium pyrrolidenedithiocarbamate, or 13-bis[2-(pyridyl)ethylidene]thiocarbonhydride. The choice of analytical method is determined by several factors, including the sample matrix available (i.e. blood, plasma, serum, tissue, milk, hair, kidney, liver, muscle, urine, or teeth), and the detection limit required (ATSDR, 2008).

Cadmium in blood is used as an indicator of both recent and cumulative exposures, and urinary cadmium predominantly reflects cumulative exposure and the concentration of cadmium in the kidney (CDC, 2005). In the general population, normal blood cadmium concentrations are in the range of 0.4–1.0 µg/L for non-smokers and 1.4–4 µg/L for smokers, although much higher levels have been reported for environmental exposure (above 10 µg/L), and occupational exposure (up to 50 µg/L) (UNEP, 2008). Women typically have higher urinary cadmium concentrations than men, in part perhaps magnified by adjustment for creatinine excretion, which is lower in women (EFSA, 2009).

In a general population survey of approximately 4700 adults in Germany, Becker *et al.* (2002, 2003) found geometric mean cadmium levels of 0.44 µg/L in blood, and 0.23 µg/L in

urine. Smokers had a blood level of 1.1 µg/L, and non-smokers a level of 0.28 µg/L. Smokers had a urine level of 0.29 µg/L, former smokers 0.25 µg/L, and never-smokers 0.18 µg/L.

A study by the Centers for Disease Control and Prevention in the USA based on data from a random sample of people (National Health and Nutrition Examination Survey 1999–2002), found that the mean blood concentration of cadmium was 0.41 µg/L (n = 7970), and the 95th percentile blood concentration was 1.3 µg/L; the mean urine concentration of cadmium was 0.91 µg/L (n = 2257), and the 95th percentile blood concentration was 1.2 µg/L (CDC, 2005). NHANES data for workers in the period 1988–94 (urinary cadmium) are presented in Section 1.5.2 (Yassin & Martonik, 2004).

In an investigation of non-occupational cadmium exposure of 52 adult women in Bangkok, Thailand, Zhang *et al.* (1999) found a geometric mean level of cadmium in blood of 0.41 µg/L and 1.40 µg/g creatinine in urine. These were the lowest when compared to four neighbouring cities in South-eastern Asia (Kuala Lumpur, 0.74 µg/L and 1.51 µg/g; Manila, 0.47 µg/L and 1.21 µg/g; Nanning, 0.71 µg/L and 1.87 µg/g; and Tainan, 0.83 µg/L and 1.59 µg/g).

2. Cancer in Humans

The previous *IARC Monograph* on cadmium and cadmium compounds conclusion was based largely on evidence of increased lung cancer risk among workers exposed to cadmium (IARC, 1993b).

2.1 Cancer of the lung

In two small copper–cadmium alloy plants in the United Kingdom, the rate of mortality from lung cancer was increased in one but decreased in the other (Holden, 1980). The follow-up was extended by Sorahan *et al.* (1995) who documented increased risks of lung cancer in vicinity workers only, and an increased risk of non-malignant diseases of the respiratory system at higher cumulative cadmium exposures [Although an increased risk of lung cancer was not documented in this study, the Working Group noted that cases of lung cancer could potentially be misclassified as non-malignant disease. There was some population overlap between these studies.]

For cadmium-processing workers from 17 plants in the United Kingdom, mortality from lung cancer was significantly increased (standardized mortality ratio [SMR], 1.12; 95%CI: 1.00–1.24), with apparent positive trends with duration of employment and with intensity of exposure (Kazantzis & Blanks, 1992). The increase in lung cancer risk was stronger in the small proportion of workers with high cadmium exposure (SMR, 1.62; 95%CI: 0.89–2.73).

Follow-up of the United Kingdom Ni–Cd battery workers confirmed a slight increase in SMR for lung cancer associated with duration of employment in high-exposure jobs (Sorahan, 1987). Although not associated with cumulative exposure to cadmium, a significant increase in the SMR for cancers of the pharynx was also seen, and a non-significantly increased SMR for lung cancer was observed (Sorahan & Esmen, 2004).

An increase in mortality rates from lung cancer was detected in a small cohort of individuals who worked in the Ni–Cd battery-producing industry in Sweden, and who had the longest duration of employment and latency (Elinder *et al.*, 1985). Further follow-up showed an SMR for lung cancer in male battery workers of 1.76 (95%CI: 1.01–2.87), although without association with estimated total cadmium exposure (Järup *et al.*, 1998).

Excess mortality from lung cancer was reported among workers employed in a US cadmium recovery plant, which had been an arsenic smelter until 1925 (Lemen *et al.*, 1976),

and a dose–response relationship was demonstrated between the estimated cumulative exposure to cadmium and lung cancer risk (Stayner *et al.*, 1993). The dose–response relationship was unlikely to be due to confounding by cigarette smoking, and the relationship persisted among workers employed after 1940, when little arsenic was present in feedstock (Stayner *et al.*, 1993). The US Occupational Safety and Health Administration (OSHA) estimated that exposure to arsenic would have resulted in no more than one case of lung cancer death in this cohort. Using detailed job histories and dust measurements from the same US plant, Sorahan & Lancashire (1997) estimated total cadmium exposure, and identified workers with and without high potential for exposure to arsenic. Relative to the workers in the lowest cumulative exposure category, increased SMRs for lung cancer were found among the workers in higher exposure categories, especially after a lag time of 10 or 20 years. However, significant excess risks of lung cancer were found only for the early years of operation, when exposures to cadmium occurred in the presence of high arsenic exposures. For workers only employed in jobs with little or no exposure to arsenic, cumulative exposure to cadmium was weakly associated with lung cancer mortality. A subsequent analysis of the arsenic-exposed component of this cohort (Sorahan, 2009) showed a statistically significant reduction in risk of lung cancer SMRs in relation to time since leaving employment with arsenic exposure. This pattern was interpreted by the author as implying a late-stage action of arsenic, and a role for arsenic and not cadmium in the causation of lung cancer in this cohort. [The Working Group found this indirect argument against a role for cadmium not to be convincing. The Working Group noted that the population overlapped between these studies.]

In Belgium, Nawrot *et al.* (2006) studied subjects residing near three zinc smelters and also subjects from the area away from the cadmium pollution for the incidence of cancer from initial examinations in 1985–89 to 2004. Using urinary cadmium excretion and cadmium in garden soil as exposure indicators, the hazard ratio for lung cancer was 1.70 (95%CI: 1.13–2.57) for a doubling of the 24-hour urinary cadmium excretion, 4.17 (95%CI: 1.21–14.4) for residence in the high-exposure area versus the low-exposure area, and 1.57 (95%CI: 1.11–2.24) for a doubling of the cadmium concentration in soil. Overall cancer was also increased in the high-exposure group. Information on smoking was included in the adjustments. Data on urinary cadmium excretion adjusted for arsenic suggested that arsenic exposure alone could not explain the observed increases in risk.

See Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-03-Table2.1.pdf

2.2 Cancer of the prostate

Following a report of the occurrence of cancer of the prostate in a small group of workers employed in a plant manufacturing Ni–Cd batteries in the United Kingdom (Potts, 1965), a series of analyses of different occupational cohorts were undertaken, which did not confirm the excess (Kipling & Waterhouse, 1967; Kjellström *et al.*, 1979; Holden, 1980; Sorahan & Waterhouse, 1983; Elinder *et al.*, 1985; Thun *et al.*, 1985; Sorahan, 1987; Kazantzis & Blanks, 1992; Sorahan & Esmen, 2004). Some of these studies reported a non-significantly increased risk for cancer of the prostate among cadmium-exposed workers, but the results were inconsistent, and mostly based on small numbers of cases. Sahmoun *et al.* (2005) calculated a weighted SMR from four studies of Ni–Cd battery production workers who were highly exposed to cadmium. The summary SMR was 1.26 (95%CI: 0.83–1.84) based on 27 deaths. [The Working Group noted that these populations overlapped.] See Table 2.2

available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-03-Table2.2.pdf.

Slightly increased odds ratios for cancer of the prostate were also reported from a case–control study nested within occupational cohorts (Armstrong & Kazantzis, 1985). A hospital-based case–control study using cadmium measurements in toenails (Vinceti *et al.*, 2007) showed a significantly increased odds ratio at the highest concentrations. A case–control study nested within a cohort did not find this association, using the same biological sample collected at baseline as the exposure measure (Platz *et al.*, 2002). [The Working Group noted that the exposure in the second study was lower than in the first, and that the cadmium concentration in toenails may represent a prediagnostic retention level of unknown validity as a measure of long-term exposure.]

A descriptive study from cadmium-polluted areas in Japan reported an increased mortality from cancer of the prostate in two of four areas studied (Shigematsu *et al.*, 1982). Using increased urinary excretion of β_2-microglobulin as a marker of cadmium toxicity within the Nagasaki Prefecture, increased cancer mortality (relative risk [RR], 2.58; 95%CI: 1.25–5.36) and cancer incidence (RR, 1.79; 95%CI: 0.84–3.82) were found among the subjects with signs of cadmium toxicity (Arisawa *et al.*, 2001, 2007). Numbers for individual cancer sites were too low to allow for detailed analysis. [The Working Group noted that these populations overlapped.]

2.3 Other cancers

Other cancer sites, such as the pancreas, show a possible excess in SMRs, but only small numbers of cases have occurred in the occupational cohorts. In a small case–control study, the OR per ng/mL change in serum cadmium concentrations was estimated as 1.12 (95%CI: 1.04–1.23) for cancer of the pancreas (Kriegel *et al.*, 2006). [The Working Group noted that the serum concentration of cadmium is a less valid measure of cadmium exposure than concentrations in urine and whole blood.]

For cancer of the kidney, small numbers were reported in two of the cohort studies without any evidence of an association with cadmium exposure (Järup *et al.*, 1998; Sorahan & Esmen, 2004), but more recent data are available from case–control studies. A German multicentre study (Pesch *et al.*, 2000) included 935 cases of renal cell carcinoma and 4298 controls, and cadmium exposure was assessed by a national job–exposure matrix (JEM). In men and women, respectively, the OR was 1.4 (95%CI: 1.1–1.8) and 2.5 (95%CI: 1.2–5.3) for high exposure and 1.4 (95%CI: 0.9–2.1) and 2.2 (95%CI: 0.6–9.0) for very high exposure. In a Canadian study of 1279 cases of renal cell carcinoma and 5370 controls, self-reported cadmium exposure was a risk factor in males (OR, 1.7; 95%CI: 1.0–3.2) (Hu *et al.*, 2002). Most recently, a German hospital-based case–control study of 134 cases of renal cell carcinoma and 401 controls reported an OR for high exposure of 1.7 (95%CI: 0.7–4.2) (Brüning *et al.*, 2003).

A hypothesis-generating case–control study in the Montréal (Canada) metropolitan area showed that the bladder was the only one of 20 cancer sites to be associated with exposure to cadmium compounds (Siemiatycki, 1991). In a case–control study of transitional cell carcinoma of the bladder, the blood cadmium concentration was measured as an indicator of long-term cadmium exposure; the highest exposure tertile showed an OR of 5.7 (95%CI: 3.3–9.9); adjustments included smoking and occupational exposures to polyaromatic hydrocarbons and aromatic amines (Kellen *et al.*, 2007).

In another study, increased cadmium concentrations were found in breast tissue, but the mean cadmium concentration found in breast cancer patients was not significantly different from that of controls (Antila *et al.*, 1996). A larger case–control study of breast cancer used urinary cadmium excretion levels as a measure

of cumulated cadmium exposure; each increase by 1.0 µg/g creatinine was associated with an OR of 2.09 (95%CI: 1.2–3.8) (McElroy *et al.*, 2006).

On the basis of food frequency questionnaires in 1987–90 and 1997, Åkesson *et al.* (2008) calculated dietary cadmium intakes; the highest tertile of cadmium exposure had an OR of 1.39 [95%CI: 1.04–1.86] for endometrial cancer in postmenopausal women. The association was stronger in never-smokers, in women with normal body mass index, and in non-users of postmenopausal hormones.

2.4 Synthesis

The assessment of cancer risks in occupational cohorts exposed to cadmium is constrained by the small number of long-term, highly exposed workers, the lack of historical data on exposure to cadmium, particularly for the non-US plants, and the inability to define and examine a gradient of cumulative exposure across studies. Confounding by cigarette smoking in relation to the assessment of lung cancer risk among cadmium-exposed workers was addressed directly only in the study from the USA. Some other studies provided analyses based on internal comparisons, which are not likely to be affected by this problem of confounding. Few studies were able to control the confounding effect of co-exposure to other substances, particularly arsenic and nickel; however, the analyses of workers with low levels of exposure to arsenic still showed an increased lung cancer risk associated with cadmium exposure. Additional support for a cadmium-linked lung cancer risk comes from a prospective population-based study in environmentally polluted areas in Belgium.

The results of the studies on cadmium exposure and the risk of prostate cancer are suggestive of an association, but the results are inconsistent. In studies of occupational cohorts exposed to cadmium, studies of people residing in cadmium-contaminated areas and case–control studies of individuals with prostate cancer, some studies reported an increased risk for prostate cancer, while other studies did not indicate the same. The results from cohort studies are supported by a hospital-based case–control study that included highly exposed subjects.

Case–control studies suggest that other cancer sites, such as the kidney, and perhaps also the bladder, the breast, and the endometrium may show increased risks associated with dietary or respiratory cadmium exposure. [The Working Group noted that although case–control studies may be subject to bias from exposure misclassification, some studies considered have the strength of inclusion of blood or urine cadmium analyses that provide individual exposure data.]

3. Cancer in Experimental Animals

Cadmium compounds have been tested for carcinogenicity by subcutaneous administration to rats, mice, and hamsters, by intramuscular injection to rats, by oral exposure to rats and mice, by intraperitoneal exposure to mice, by inhalation exposure to rats, mice and hamsters, and by intratracheal administration to rats.

Particularly relevant studies reviewed in the previous *IARC Monograph* (IARC, 1993b) were reconsidered in this evaluation.

All cadmium compounds tested were not carcinogenic by all routes tested but most studies performed provided evidence for cadmium-induced carcinogenicity in animals.

3.1 Oral administration

Oral administration of cadmium chloride to rats increased the incidence of large granular lymphocytes, leukaemia, prostate tumours, and testis tumours in Wistar rats (Waalkes & Rehm, 1992). Noble rats exposed to oral cadmium chloride developed prostate hyperplasia (Waalkes *et al.*, 1999b).

See Table 3.1.

Table 3.1 Studies of cancer in experimental animals exposed to cadmium (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar WF/NCr (M) 77 wk Waalkes & Rehm (1992)	Cadmium chloride 0, 25, 50, 100 or 200 ppm in diet Also fed previous diets with zinc levels of 60 ppm (zinc adequate), 7 ppm (zinc deficient) for 2 wk 28/group 56 pooled controls	Prostate (tumours): 4/26 (15%) cadmium (50ppm) vs 1/54 (2%) pooled controls High-dose cadmium + zinc deficient: Testis (tumours)– 6/27 (22%) vs 1/28 (3%) controls Leukaemia (LGL): 7/25 (28%) vs pooled controls 3/55 (5%)	$P < 0.05$ $P < 0.05$	Age at start, 2 wk Prostate tumours not affected by zinc deficiency unless combined with prostate hyperplasias No increase in testis tumours with cadmium alone
Rat, Noble NBL/Cr (M) 102 wk Waalkes *et al.* (1999b)	Cadmium chloride 0, 25, 50, 100, 200 ppm in drinking-water 30/group	Prostate (dorsolateral and ventral; hyperplasias): 6 (21%), 12 (46%), 13 (50%), 6 (21%), 4 (15%) Testis (tumours): 2/29 (7%), 2/30 (7%), 3/30 (10%), 4/30 (13%), 5/28 (18%) Adrenal gland (pheochromocytomas): 2 (7%), 3 (10%), 8 (27%), 6 (20%), 3 (10%)	$P < 0.05$ vs control (Groups 2 & 3) NR $P < 0.05$ (mid-dose)	Age at start, 10 wk No dose response to induction of any tumour type

d, day or days; h, hour or hours; mo, month or months; LGL, large granular lymphocyte; NR, not reported; NS, not significant; vs, versus; wk, week or weeks

3.2 Inhalation and intratracheal administration

3.2.1 Rat

Inhalation exposure to cadmium chloride caused lung tumours in rats (Takenaka *et al.*, 1983; Glaser *et al.*, 1990). Cadmium sulfate, cadmium oxide, cadmium oxide fume and dust also caused lung tumours in rats (Glaser *et al.*, 1990).

Intratracheal administration of cadmium chloride and cadmium sulfide caused lung tumours in rats (Oberdörster & Cherian, 1992).

3.2.2 Hamster

Cadmium chloride, cadmium sulfate, cadmium sulfide, and cadmium oxide fume did not cause lung tumours in hamsters (Heinrich *et al.*, 1989; Heinrich, 1992).

See Table 3.2.

3.3 Subcutaneous administration

Many of the earliest carcinogenicity studies with cadmium compounds in rodents involved subcutaneous or intramuscular administration. In most studies, injection-site sarcomas developed in rats and mice. Mice were generally less susceptible than were rats. The earlier studies are reviewed in the previous *IARC Monograph*, and are not reviewed here, in part, because larger and better designed studies were published after 1993.

3.3.1 Mouse

Subcutaneous administration of cadmium chloride caused lymphomas, lung tumours (Waalkes & Rehm, 1994), and injection-site sarcomas (Waalkes *et al.*, 1991a; Waalkes & Rehm, 1994) in mice.

3.3.2 Rat

Subcutaneous administration of cadmium chloride caused injection-site sarcomas (Waalkes *et al.*, 1988, 1989, 1991b, 1997, 1999a, 2000; IARC, 1993b; Shirai *et al.*, 1993), and testis (interstitial cell) tumours in rats (Waalkes *et al.*, 1988, 1989, 1997, 1999b, 2000). Cadmium chloride caused prostate tumours and/or preneoplastic lesions in Wistar and Noble rats (Waalkes *et al.*, 1988, 1999b), but not in other studies in F344 or Wistar Furth rats (Waalkes *et al.*, 1991c, 2000; Shirai *et al.*, 1993).

3.3.3 Hamster

A single injection of cadmium chloride did not induce tumours in hamsters (Waalkes & Rehm, 1998).

A variety of cadmium compounds and metallic cadmium caused local sarcomas in rats or mice (IARC, 1993b).

See Table 3.3.

3.4 Administration with known carcinogens or other agents

The incidence of injection-site sarcomas in Wistar rats induced by cadmium chloride was significantly reduced by both the subcutaneous and oral administration of zinc (Waalkes *et al.*, 1989). Testicular tumours induced by subcutaneously administered cadmium chloride were inhibited by zinc, and were found to be associated with a reduction of the chronic degenerative testicular lesions induced by cadmium chloride (Waalkes *et al.*, 1989).

Testosterone implantation eliminated both cadmium-induced and spontaneous testis tumours in F344 rats but had no effect on cadmium-induced chronic testicular degeneration (Waalkes *et al.*, 1997).

Table 3.2 Studies of cancer in experimental animals exposed to cadmium (inhalation and intratracheal exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Inhalation				
Rat, Wistar, TNO/W75 (M) 31 mo Takenaka *et al.* (1983)	Cadmium chloride 12.5, 25 or 50 μg/m³, 23 h/d, 7 d/wk for 18 mo 40/group	Lung (adenocarcinomas): 0/38, 6/39 (15%), 20/38 (52%), 25/35 (71%)	[$P < 0.0001$; Groups 3 & 4]	Age at start, 6 wk
Rat, Wistar, TNO/W75 > BOR-WISW (M, F) 31 mo Glaser *et al.* (1990)	0 to 900 μg/m³ of cadmium chloride, cadmium sulfate, cadmium oxide, cadmium oxide fume, zinc oxide dust, and cadmium oxide dust, 40 h/wk for 18 mo Groups of 20–40 males, 20 females	All forms increased lung tumour incidence, 18/20 (90%) in cadmium sulfate females, 0/20 in controls from 31 experimental groups Controls, males 0/40, females 0/20 High doses > 75% incidences	[$P < 0.0001$]	Age at start, 9 wk Problem with concentration of cadmium in cadmium oxide fume Data from 31 experimental groups in Table 13, p.166, Volume 58 (IARC, 1993b)
Intratracheal				
Rat, Wistar (F) 124 wk Oberdörster & Cherian (1992)	Cadmium chloride or cadmium oxide 20 weekly 1 or 3 μg or 15 weekly 9 μg Cadmium sulfide 10 weekly 63, 250 or 1000 μg (purity 99%) Controls received 20x0.3ml saline	Lung (tumours): Cadmium chloride– Controls, 0/40; 20, 0/38; 60, 3/40 (7%); 135, 2/36 (6%) Cadmium oxide– 20, 2/37 (5%); 60, 2/40 (5%); 135, 0/39 Cadmium sulfide– 630, 2/39 (5%); 2500, 8/36 (22%); 10000, 7/36 (19%)	$P < 0.01$ trend test NS $P = 0.0005$ trend test	Cadmium chloride and cadmium sulfide purity, 99%

d, day or days; h, hour or hours; mo, month or months; NR, not reported; NS, not significant; wk, week or weeks

Table 3.3 Studies of cancer in experimental animals exposed to cadmium (subcutaneous or intramuscular exposure; for years < 1993, only selected references included)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar Crl WI BR (M) 104 wk Waalkes *et al.* (1988)	Cadmium chloride Single s.c. 0, 1, 2.5, 5, 10, 20, or 40 µmol/kg bw; 5 µmol/kg 4 × 5 and 10 µmol/kg 1 × each, 5 and 20 µmol/kg 1 × each (time 0 (low dose) and 48 h (high dose)) 30/group 45 pooled controls	Injection site (mostly sarcomas, also fibromas, epithelial tumours): 2/45 (4%), 1/30 (3%), 0/29, 1/30 (3%), 2/30 (7%), 1/29 (3%), *14/30 (47%) 0/30, 1/30 (3%), *8/30 (27%)	$P < 0.05$ from pooled control	Age at start, 6 wk High dose cadmium reduced testicular tumour responses Prostate tumour response is not strong or a dose response
		Testis (tumours): 8/45 (18%), 1/30 (3%), 3/29 (10%), 3/30 (10%), 4/30 (13%), *21/29 (72%), *24/29 (83%) 4/30 (13%), 2/30 (7%), 5/30 (17%)	$P < 0.05$	
		Prostate (ventral lobe; tumours): 5/44 (11%), 6/27 (22%), *8/26 (31%), 4/28 (14%), 4/23 (17%), 4/26 (15%), 3/29 (10%) 2/26 (8%), 5/28 (18%), 6/28 (21%)	$P < 0.05$ from pooled control	
		Preneoplastic foci: Positive trend with single dose (data in chart)	NR	
		Pancreas (acinar and islet cell): Negative trend with dose	NR	

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar (M) 104 wk Waalkes *et al.* (1989)	Cadmium chloride Single injection s.c. 30 µmole/kg 3 × zinc acetate 0.1, 0.3, 1.0 mmol/kg i.m. 30 mmole/kg cadmium chloride + zinc chloride 1 mmol/kg + zinc acetate in water 30/group	Injection site (sarcomas): 12/30 (40%), pooled controls 0/84 1 × zinc reduced incidence	$P < 0.05$	
		Testis (tumours): Cd 1 × 25/30 (83%), controls 9/83 (11%) Zinc, dose-dependent decrease	$P < 0.05$	
		Prostate (adenoma): i.m. Cd 11/26 (42%), Cd+zinc 8/27 (30%), i.m. Cd+s.c. zinc 7/28 (25%), controls 8/83 (10%)	$P < 0.05$	
Rat, F344 (M) 104 wk Waalkes *et al.* (1997)	Cadmium chloride 20 µmole/kg s.c. once/wk for 5 wk Testosterone implants, 10 interim sacrifices 50/group	Testis (tumours): Controls 24/40 (60%)		Age at start, 10 wk
		Testosterone only *0/40 Cd only *34/40 (98%)	*$P \leq 0.05$ from control	
		Testosterone+Cd *†0/37	†$P \leq 0.05$ from cadmium alone	
Rat, Noble, NBL/Cr (M) 72 wk Waalkes *et al.* (1999a)	Cadmium chloride Single injection s.c. 0, 1, 2, 4, 8, 16, 32 µmole/kg 30/group	Testis: 1/30 (3%), 0/30, 0/30, 1/30 (3%), 7/30 (23%), 29/30 (96%), 28/30 (93%)	$P < 0.053$ (higher doses)	Prostate hyperplasia only
		Injection site (sarcomas): 0/30, 0/30, 0/30, 0/30, 0/30, 0/30, 7/30 (22%), 11/30 (37%)	$P < 0.05$	
		Prostate (proliferative lesions): 9/25 (36%), 16/26 (62%), 19/29 (65%), 19/24 (79%), 17/27 (63%), 18/30 (60%), 15/29 (52%)	$P < 0.05$, three middle doses	

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, WF/NCr, F344/NCr (M) 104 wk Waalkes *et al.* (2000)	Cadmium chloride Single injection, s.c. 0, 10, 20, 30 µmole/kg bw weekly for 18 wk, 3 µmole/kg 1 wk then weekly 17 × 30 µmole/kg 30/group	Injection site (sarcomas): WF–0/20, 1/29 (3%), 21/29 (72%), 23/28 (82%), 23/29 (79%) F344–0/30, 11/30 (37%), 17/30 (68%), 8/12 (67%), 18/30 (60%)	$P < 0.05$ WF, four highest doses; F344 all doses	No prostate tumours were reported
		Testis: WF–11/29 (38%), 27/29 (93%), 19/29 (65%), 15/28 (54%), 15/29 (52%) F344–29/30 (97%), 28/30 (93%), 14/25 (56%), 8/12 (67%), 12/30 (43%)	$P < 0.05$ WF, two lower doses; F344 reduction in three highest doses	Pituitary adenomas reduced in higher doses of WF rats
Mouse, DBA/2NCr, NFS/NCr 104 wk (Waalkes & Rehm, 1994)	Cadmium chloride 40 µmol/kg s.c. 1once or once/wk for 16 wk 30–40/group	Lymphomas: DBA–1X Cd, 11/23 (48%); 16 × Cd, *16/28 (57%) Controls, 7/27 (26%)	$P = 0.024$ trend test	Age, 8 wk Strain differences seen No testis tumours
		Injection site (sarcomas): NFS–1X Cd, 3/27 (11%); 16 × Cd, 3/32 (9%) Controls, 0/23	$P = 0.016$ trend test	
		Lung: NFS–1X Cd, *21/28 (75%); 16 × Cd, 9/35 (26%) Controls, 6/25 (24%)		

h, hour or hours; i.m., intramuscular; NR, not reported; s.c., subcutaneous; wk, week or weeks

3.5 Synthesis

By inhalation, various cadmium compounds induce lung tumours in rats (cadmium chloride, cadmium oxide, cadmium oxide dust, cadmium oxide fumes, cadmium sulfide). Intratracheal administration of cadmium chloride and cadmium sulfide induces lung tumours in rats. In one study, subcutaneous injection of cadmium chloride caused lung tumours in mice. A variety of cadmium compounds and metallic cadmium cause local sarcomas in rats or mice. Administration of various salts of cadmium causes testicular tumours in rats. Cadmium chloride induced prostatic proliferative lesions and testicular tumours in rats after subcutaneous or oral administration.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

Inhalation is the major route of cadmium exposure in occupational settings, whereas most people in the general population are exposed to cadmium via the ingestion of both food and drinking-water. Exposure to cadmium particulates lead to cadmium absorption in animals and humans (IARC, 1993b).

In occupational settings, cadmium and cadmium compounds, being non-volatile, exist in air as fine particulates. Animal studies (Rusch *et al.*, 1986) have shown that lung retention may be up to 20%, especially after short-term exposure.

When ingested, most of the cadmium passes through the gastrointestinal tract without being absorbed. Estimates of the cadmium absorption rate in humans have been reported as 3–5% (Morgan & Sherlock, 1984) or 6.5% (Horiguchi *et al.*, 2004). Even lower rates have been reported for experimental animals, especially after long-term repeated exposures (Schäfer *et al.*, 1990).

When absorbed, cadmium will bind to metallothionein, forming a cadmium–metallothionein complex that is transferred (via blood) primarily to the liver and the kidney (Waalkes & Goering, 1990). Metallothionein is inducible in different tissues (e.g. liver, kidney, intestine, and lung) by exposure to various agents including cadmium (Waalkes & Goering, 1990). When transported to the kidney, cadmium–metallothionein is readily filtered at the glomerulus, and may be efficiently reabsorbed from the filtrate in the proximal tubules (Foulkes, 1978; Dorian *et al.*, 1992a). In the tubules, the protein portion is rapidly degraded to release cadmium (Dorian *et al.*, 1992b). Cadmium accumulates in kidney tubules, and causes damage to tubular cells, especially in the proximal tubules (Kasuya *et al.*, 1992).

Absorbed cadmium is excreted very slowly, and the amounts excreted into urine and faeces are approximately equal (Kjellström & Nordberg, 1978). In humans, half-life estimates are in the range of 7–16 years (Kjellström & Nordberg, 1978; Nordberg *et al.*, 2007).

4.2 Genetic and related effects

In rodent experiments, cadmium salts cause increased frequencies of micronuclei and chromosomal aberrations. In mammalian cells *in vitro*, cadmium compounds cause DNA strand breaks and chromosomal aberrations, and are weakly mutagenic, whereas in most bacterial assays, cadmium compounds are not mutagenic (Waalkes, 2003; DFG, 2006). Both soluble and insoluble cadmium compounds generally give comparable results in genotoxicity assays when tested in parallel.

Because cadmium salts do not cause DNA damage in cell extracts or with isolated DNA (Valverde *et al.*, 2001), the genotoxicity of cadmium has to be explained by indirect mechanisms. Frequently discussed mechanisms are related to oxidative stress, the inhibition of

DNA-repair systems, effects on cell proliferation, and on tumour-suppressor functions.

4.2.1 Induction of oxidative stress

Even though cadmium is not redox-active, it has been shown to induce oxidative stress, both *in vitro* and *in vivo*. Cadmium sulfide induced hydrogen peroxide formation in human polymorphonuclear leukocytes, and cadmium chloride enhanced the production of superoxide in rat and human phagocytes (Sugiyama, 1994). The induction of DNA strand breaks and chromosomal aberrations by cadmium in mammalian cells is suppressed by antioxidants and antioxidative enzymes (Ochi *et al.*, 1987; Stohs *et al.*, 2001; Valko *et al.*, 2006). Because cadmium does not undergo redox reactions under physiological conditions, the increased generation of reactive oxygen species levels and oxidative cellular damage may be due to the inhibitory effect of cadmium on antioxidant enzymes (Stohs *et al.*, 2001; Valko *et al.*, 2006) as well as on DNA-repair systems.

4.2.2 Inhibition of DNA repair

Cadmium is co-mutagenic and increases the mutagenicity of ultraviolet radiation, alkylation, and oxidation in mammalian cells. These effects are explained by the observation that cadmium inhibits several types of DNA-repair mechanisms, i.e. base excision, nucleotide excision, mismatch repair, and the elimination of the pre-mutagenic DNA precursor 7,8-dihydro-8-oxoguanine (Hartwig & Schwerdtle, 2002). In base-excision repair, low concentrations of cadmium that do not generate oxidative damage as such, very effectively inhibit the repair of oxidative DNA damage in mammalian cells (Dally & Hartwig, 1997; Fatur *et al.*, 2003). In nucleotide-excision repair, cadmium interferes with the removal of thymine dimers after UV irradiation by inhibiting the first step of this repair pathway, i.e. the incision at the DNA lesion (Hartwig & Schwerdtle, 2002; Fatur *et al.*, 2003). Furthermore, chronic exposure of yeast to very low cadmium concentrations results in hypermutability; and in human cell extracts, cadmium has been shown to inhibit DNA-mismatch repair (Jin *et al.*, 2003). Additionally, cadmium disturbs the removal of 8-oxo-dGTP from the nucleotide pool by inhibiting the 8-oxo-dGTPases of bacterial and human origin (Bialkowski & Kasprzak, 1998).

One molecular mechanism related to the inactivation of DNA-repair proteins involves the displacement by cadmium of zinc from zinc-finger structures in DNA-repair proteins such as xeroderma pigmentosum group A (XPA), which is required for nucleotide-excision repair, and formamidopyrimidine-DNA-glycosylase (Fpg), which is involved in base-excision repair in *E. coli* (Asmuss *et al.*, 2000). Cadmium also inhibits the function of human 8-oxoguanine-DNA-glycosylase (hOGG1), which is responsible for recognition and excision of the pre-mutagenic 7,8-dihydro-8-oxoguanine during base-excision repair in mammalian cells (Potts *et al.*, 2003). Even though hOGG1 contains no zinc-binding motif itself, the inhibition of its function is due to its downregulation as a result of diminished DNA-binding of the transcription factor SP1 that contains zinc-finger structures (Youn *et al.*, 2005). Finally, cadmium induces a conformational shift in the zinc-binding domain of the tumour-suppressor protein p53. Thus, in addition to inhibiting repair proteins directly, cadmium downregulates genes involved in DNA repair *in vivo* (Zhou *et al.*, 2004).

The impact of cadmium on DNA repair may be especially deleterious in cadmium-adapted cells. Cadmium induces several genes for cadmium and reactive oxygen species tolerance such as those coding for metallothionein, glutathione synthesis and function, catalase and superoxide dismutase (Stohs *et al.*, 2001). Hence, a condition for prolonged cell survival in the

presence of cadmium is established (Chubatsu *et al.*, 1992). Taking into account the impact of cadmium on DNA repair, tolerance to cadmium toxicity concurrently may constitute a greater opportunity for the induction of further critical mutations (Achanzar *et al.*, 2002).

4.2.3 Deregulation of cell proliferation and disturbance of tumour-suppressor functions

Cadmium interacts with a multitude of cellular signal transduction pathways, many of which associated with mitogenic signalling. Submicromolar concentrations of cadmium stimulated DNA synthesis, and the proliferation of rat myoblast cells (von Zglinicki *et al.*, 1992) and of rat macrophages (Misra *et al.*, 2002). In various cell types *in vitro*, cadmium induces the receptor-mediated release of the second messengers inositol-1,4,5-trisphosphate and calcium, activates various mitogenic protein kinases, transcription and translation factors, and induces the expression of cellular proto-oncogenes, *c-fos*, *c-myc*, and *c-jun* (Waisberg *et al.*, 2003). However, it should be noted that the activation of mitogen-activated protein kinases is not a sufficient condition for enhanced cell proliferation, because persistent low-dose exposure of cells to cadmium has been shown to result in sustained activation of protein kinase ERK, but also to caspase activation and apoptosis (Martin *et al.*, 2006). In addition to directly stimulating mitogenic signals, cadmium also inhibits the negative controls of cell proliferation. It inactivates the tumour-suppressor protein p53, and inhibits the p53 response to damaged DNA (Méplan *et al.*, 1999). This finding could be particularly important to explain the carcinogenicity of cadmium because p53 is required for cell-cycle control, DNA repair, and apoptosis; its inactivation would be expected to lead to genomic instability.

It was also reported that cadmium modulates steroid-hormone-dependent signalling in ovaries in rats, in a breast cancer cell line, and in cadmium-transformed prostate epithelial cells (Benbrahim-Tallaa *et al.*, 2007a; Brama *et al.*, 2007). Nevertheless, in in-vitro estrogenicity assays based on estrogen-receptor activity, no effect of cadmium was detected (Silva *et al.*, 2006). Whether or not cadmium promotes tumour growth by an estrogen-mediated mechanism is still unknown.

In addition to effects on genes and genetic stability, cadmium also exerts epigenetic effects, which may contribute to tumour development. During cadmium-induced cellular transformation, DNA–(cytosine-5) methyltransferase activity and global DNA methylation were reduced after 1 week of exposure to cadmium (Takiguchi *et al.*, 2003). Prolonged exposure to cadmium (~10 weeks) resulted in enhanced DNA–methyltransferase activity, and global DNA hypermethylation in these cells (Takiguchi *et al.*, 2003), and in human prostate epithelial cells (Benbrahim-Tallaa *et al.*, 2007b). Changes in DNA methylation is thought to have a tumour-promoting effect because a decrease in DNA methylation is associated with increased expression of cellular proto-oncogenes, and an increase of DNA methylation results in the silencing of tumour-suppressor genes.

4.3 Synthesis

Several mechanisms have been identified that potentially contribute to cadmium-induced carcinogenesis. Direct binding to DNA appears to be of minor importance, and mutagenic responses are weak. Convincing evidence exists on disturbances of DNA-repair and tumour-suppressor proteins, which lead to chromosomal damage and genomic instability. Further reported effects include changes in DNA-methylation patterns as well as interactions with signal-transduction processes, which may contribute to the deregulation of cell growth. However, it is not yet possible to assess the relative contributions of these latter mechanisms for cancer in humans.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of cadmium and cadmium compounds. Cadmium and cadmium compounds cause cancer of the lung. Also, positive associations have been observed between exposure to cadmium and cadmium compounds and cancer of the kidney and of the prostate.

There is *sufficient evidence* in experimental animals for the carcinogenicity of cadmium compounds.

There is *limited evidence* in experimental animals for the carcinogenicity of cadmium metal.

Cadmium and cadmium compounds are *carcinogenic to humans (Group 1).*

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CHROMIUM (VI) COMPOUNDS

Chromium (VI) compounds were considered by previous IARC Working Groups in 1972, 1979, 1982, 1987, and 1989 (IARC, 1973, 1979, 1980, 1982, 1987, 1990). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms, trade names, and molecular formulae for selected chromium (VI) compounds are presented in Table 1.1. This list is not exhaustive, nor does it necessarily reflect the commercial importance of the various chromium-containing substances. Rather, it is indicative of the range of chromium (VI) compounds available.

1.2 Chemical and physical properties of the agents

Chromium (VI), also known as hexavalent chromium, is the second most stable oxidation state of chromium. Rarely occurring naturally, most chromium (VI) compounds are manufactured (products or by-products). Chromium (VI) can be reduced to the more stable chromium (III) in the presence of reducing agents (e.g. iron) or oxidizable organic matter (OSHA, 2006). Selected chemical and physical properties of various chromium (VI) compounds are presented in the previous *IARC Monograph* (IARC, 1990).

Chromium (VI) compounds are customarily classed as soluble or insoluble in water. Examples of water-soluble chromium (VI) compounds are sodium chromate (873 g/L at 30 °C) and potassium chromate (629 g/L at 20 °C). Water-insoluble chromium (VI) compounds include barium chromate (2.6 mg/L at 20 °C), and lead chromate (0.17 mg/L at 20 °C) (Lide, 2008). Compounds with solubilities in the middle of this range are not easily classified, and technical-grade compounds, such as the various zinc chromates, can have a wide range of solubilities (IARC, 1990). In the United States of America, the Occupational Safety and Health Administration (OSHA) has divided chromium (VI) compounds and mixtures into the following three categories: water-insoluble (solubility < 0.01 g/L), slightly soluble (solubility 0.01 g/L–500 g/L), and, highly water-soluble (solubility ≥ 500 g/L) (OSHA, 2006).

Chromium (VI) compounds are mostly lemon-yellow to orange to dark red in colour. They are typically solid (i.e. crystalline, granular, or powdery) although one compound (chromyl chloride) is a dark red liquid that decomposes into chromate ion and hydrochloric acid in water (OSHA, 2006).

Table 1.1 Chemical names (CAS names are given in italics), synonyms, and molecular formulae of selected chromium (VI) compounds

Chemical name	CAS No.[a]	Synonyms	Formula[b]
Ammonium chromate	7788-98-9	Chromic acid, ammonium salt; *chromic acid (H_2CrO_4), diammonium salt*; diammonium chromate	$(NH_4)_2CrO_4$
Ammonium dichromate	7789-09-5	Ammonium bichromate; ammonium chromate; *chromic acid ($H_2Cr_2O_7$), diammonium salt*; diammonium dichromate; dichromic acid, diammonium salt	$(NH_4)_2Cr_2O_7$
Barium chromate	10294-40-3 (12000-34-9; 12 231-18-4)	Barium chromate (VI); barium chromate (1:1); barium chromate oxide; *chromic acid (H_2CrO_4), barium salt (1:1)*	$BaCrO_4$
Basic lead chromate	1344-38-3 (54692-53-4)	C.I. 77 601; *C.I. Pigment Orange 21*; C.I. Pigment Red; lead chromate oxide	$PbO.PbCrO_4$
Calcium chromate	13765-19-0	Calcium chromium oxide; calcium monochromate; *chromic acid (H_2CrO_4), calcium salt (1:1)*; C.I. 77223; C.I. Pigment Yellow 33	$CaCrO_4$
Chromium [VI] chloride	14986-48-2	Chromium hexachloride; *(OC-6–11)-chromium chloride ($CrCl_6$)*	$CrCl_6$
Chromium trioxide	1333-82-0 (12324-05-9; 12324-08-2)	Chromia; chromic acid; chromic (VI) acid; chromic acid, solid; chromic anhydride; chromic trioxide; *chromium oxide (CrO3)*; chromium (VI) oxide; chromium (6+) trioxide; monochromium trioxide	CrO_3
Chromyl chloride	14977-61-8	Chlorochromic anhydride; chromium chloride oxide; chromium dichloride dioxide; *chromium, dichlorodioxo-(T-4)*; chromium dioxide dichloride; chromium dioxychloride; chromium oxychloride; dichlorodioxochromium	CrO_2Cl_2
Lead chromate	7758-97-6 (8049-64-7) 1344-37-2	*Chromic acid (H_2CrO_4), lead (2+) salt (1:1)*; C.I. 77600; C.I. Pigment Yellow 34; Chrome Yellow; lead chromate/lead sulfate mixture	$PbCrO_4$
Molybdenum orange	12656-85-8	*C.I. Pigment Red 104*; lead chromate molybdate sulfate red	$PbMoO_4$ $PbCrO_4$ $PbSO_4$
Potassium chromate	7789-00-6	Bipotassium chromate; *chromic acid (H_2CrO_4), dipotassium salt*; dipotassium chromate; dipotassium monochromate; neutral potassium chromate; potassium chromate (VI)	K_2CrO_4
Potassium dichromate	7778-50-9	*Chromic acid ($H_2Cr_2O_7$), dipotassium salt*; dichromic acid, dipotassium salt; dipotassium bichromate; dipotassium dichromate; potassium bichromate; potassium dichromate (VI)	$K_2Cr_2O_7$
Sodium chromate	7775-11-3	*Chromic acid (H_2CrO_4), disodium salt*; chromium disodium oxide; chromium sodium oxide; disodium chromate; neutral sodium chromate; sodium chromium oxide	Na_2CrO_4

Table 1.1 (continued)

Chemical name	CAS No.[a]	Synonyms	Formula[b]
Sodium dichromate	10588-01-9 (12018-32-5)	Bichromate of soda; *chromic acid ($H_2Cr_2O_7$), disodium salt*; chromium sodium oxide; dichromic acid, disodium salt; disodium dichromate; sodium bichromate; sodium dichromate (VI)	$Na_2Cr_2O_7$
Strontium chromate	7789-06-2 (54322-60-0)	*Chromic acid (H_2CrO_4), strontium salt (1:1)*; C.I. Pigment Yellow 32; strontium chromate (VI); strontium chromate (1:1)	$SrCrO_4$
Zinc chromate[c]	13530-65-9 (1308-13-0; 1328-67-2; 14675-41-3)	*Chromic acid (H_2CrO_4), zinc salt (1:1)*; chromium zinc oxide; zinc chromium oxide; zinc tetraoxychromate; zinc tetroxychromate	$ZnCrO_4$
Zinc chromate hydroxides	15930-94-6 (12206-12-1; 66516-58-3)	Basic zinc chromate; chromic acid (H_6CrO_6), zinc salt (1:2); chromic acid (H_4CrO_5), zinc salt (1:2), monohydrate; chromium zinc hydroxide oxide; zinc chromate hydroxide; zinc chromate (VI) hydroxide; *zinc chromate oxide ($Zn_2(CrO_4)O$), monohydrate*; zinc hydroxychromate; zinc tetrahydroxychromate; zinc yellow[d]	$Zn_2CrO_4(OH)_2$ and others
Zinc potassium chromates (hydroxides)	11103-86-9 (12527-08-1; 37809-34-0)	Basic zinc potassium chromate; chromic acid ($H_6Cr_2O_9$), potassium zinc salt (1:1:2); *potassium hydroxyoctaoxodizincate dichromate (1-)*; potassium zinc chromate hydroxide; zinc yellow[d]	$KZn_2(CrO_4)_2(OH)$ and others

[a] Replaced CAS Registry numbers are given in parentheses.
[b] Compounds with the same synonym or trade name can have different formulae.
[c] The term 'zinc chromate' is also used to refer to a wide range of commercial zinc and zinc potassium chromates.
[d] 'Zinc yellow' can refer to several zinc chromate pigments; it has the CAS No. 37300-23-5.

1.3 Use of the agents

Chromium (VI) compounds are used widely in applications that include: pigment for textile dyes (e.g. ammonium dichromate, potassium chromate, sodium chromate), as well as for paints, inks, and plastics (e.g. lead chromate, zinc chromate, barium chromate, calcium chromate, potassium dichromate, sodium chromate); corrosion inhibitors (chromic trioxide, zinc chromate, barium chromate, calcium chromate, sodium chromate, strontium chromate); wood preservatives (chromium trioxide); metal finishing and chrome plating (chromium trioxide, strontium chromate), and leather tanning (ammonium dichromate). Chromium (VI) may be present as an impurity in Portland cement, and it can be generated and given off during casting, welding, and cutting operations (for example, of stainless steel), even if it was not originally present in its hexavalent state (NTP, 2005; OHCOW, 2005; OSHA, 2006).

1.4 Environmental occurrence

Chromium (VI) can occur naturally in the earth's crust, although it is primarily emitted to the environment as a result of anthropogenic activities. The occurrence and distribution of chromium in the environment has been extensively reviewed (Mukherjee, 1998; Kotaś & Stasicka, 2000; Rowbotham *et al.*, 2000; Ellis *et al.*, 2002; Paustenbach *et al.*, 2003; Guertin *et al.*, 2004; Reinds *et al.*, 2006; Krystek & Ritsema, 2007).

1.4.1 Natural occurrence

Only lead chromate (as crocoite) and potassium dichromate (as lopezite) are known to occur in nature (IARC, 1990).

1.4.2 Air

Chromium (VI) is reported to account for approximately one third of the 2700–2900 tons of chromium emitted to the atmosphere annually in the USA (ATSDR, 2008a). Based on US data collected from 2106 monitoring stations during 1977–84, the arithmetic mean concentrations of total chromium in the ambient air (urban, suburban, and rural) were in the range of 0.005–0.525 μg/m^3 (ATSDR, 2000).

1.4.3 Water

The concentration of chromium in uncontaminated waters is extremely low (< 1 μg/L or < 0.02 μmol/L). Anthropogenic activities (e.g. electroplating, leather tanning) and leaching of wastewater (e.g. from sites such as landfills) may cause contamination of the drinking-water (EVM, 2002). Chromium (VI) has been identified in surface water (n = 32) and groundwater samples (n = 113) collected from 120 hazardous waste sites in the USA (ATSDR, 2000), and 38% of municipal sources of drinking-water in California, USA, reportedly have levels of chromium (VI) greater than the detection limit of 1 μg/L (Sedman *et al.*, 2006).

1.4.4 Soil

Chromium is present in most soils in its trivalent form, although chromium (VI) can occur under oxidizing conditions (ATSDR, 2008a). In the USA, the geometric mean concentration of total chromium was 37.0 mg/kg (range, 1.0–2000 mg/kg) based on 1319 samples collected in coterminous soils (ATSDR, 2000).

1.4.5 Food

There is little information available on chromium (VI) in food. Most of the chromium ingested with food is chromium (III) (EVM, 2002).

1.4.6 Smoking

Tobacco smoke contains chromium (VI), and indoor air polluted by cigarette smoke can contain hundreds of times the amount of chromium (VI) found in outdoor air.

1.5 Human exposure

1.5.1 Exposure of the general population

The general population residing in the vicinity of anthropogenic sources of chromium (VI) may be exposed through inhalation of ambient air or ingestion of contaminated drinking-water (ATSDR, 2000).

1.5.2 Occupational exposure

Inhalation of dusts, mists or fumes, and dermal contact with chromium-containing products are the main routes of occupational exposure. Industries and processes in which exposure to chromium (VI) occurs include: production, use and welding of chromium-containing metals and alloys (e.g. stainless steels, high-chromium steels); electroplating; production and use of chromium-containing compounds, such as pigments, paints (e.g. application in the aerospace industry and removal in construction and maritime industries), catalysts, chromic acid, tanning agents, and pesticides (OSHA, 2006).

Occupational exposures to several specific chromium compounds are reported in the previous *IARC Monograph* (IARC, 1990). With respect to chromium (VI) compounds, the most important exposures have been to sodium, potassium, calcium, and ammonium chromates and dichromates during chromate production; to chromium trioxide during chrome plating; to insoluble chromates of zinc and lead during pigment production and spray painting; to water-soluble alkaline chromates during steel smelting and welding; and, to other chromates during cement production and use (see Table 10; IARC, 1990, and OHCOW, 2005) for lists of occupations potentially exposed to chromium (VI)).

Estimates of the number of workers potentially exposed to chromium (VI) compounds have been developed by CAREX (CARcinogen EXposure) in Europe. Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX database estimates that 785692 workers were exposed to hexavalent chromium compounds in the European Union, with over 58% of workers employed in the following four industries: manufacture of fabricated metal products except machinery and equipment (n = 178329), manufacture of machinery except electrical (n = 114452), personal and household services (n = 85616), and manufacture of transport equipment (n = 82359). CAREX Canada (2011) estimates that 83000 Canadians are occupationally exposed to chromium (VI) compounds. Industries in which exposure occurred include: printing and support activities; architectural/structure metal manufacturing; agricultural, construction, mining machinery manufacturing; specialty trade contractors; boiler, tank, and container manufacturing; industrial machinery repair; auto repair; metalworking machinery manufacturing; steel product manufacturing; aluminum production; metal ore mining; coating, engraving, and heat treating. Welders were the largest occupational group exposed (n = 19100 men and 750 women).

Data on early occupational exposures to chromium (VI) are summarized in the previous *IARC Monograph* (IARC, 1990). Data from studies on chromium (VI) exposure published since the previous *IARC Monograph* are summarized below.

In a study to characterize occupational exposure to airborne particulate containing chromium, and to evaluate existing control technologies, the US National Institute for Occupational Safety and Health (NIOSH) conducted 21 field surveys during 1999–2001 in selected industries. Industries and operations

evaluated included: chromium electroplating facilities; welding in construction; metal cutting operations on chromium-containing materials in ship breaking; chromate-paint removal with abrasive blasting; atomized alloy-spray coating; foundry operations; printing; and the manufacture of refractory brick, coloured glass, prefabricated concrete products, and treated wood products. Personal breathing zone samples (full-shift and short-term) and general area samples were collected. Results were compared to the NIOSH recommended exposure limit (REL) of 1 μg/m^3 (for a 10-hour exposure). Full-shift personal exposures to chromium (VI) were in the range of 3.0–16 μg/m^3 at the electroplating facilities, and 2.4–55 μg/m^3 at a painting and coating facility that used products containing chromium (VI) (Blade *et al.*, 2007).

NIOSH conducted a health hazard evaluation of worker exposures during the welding and manufacturing of stainless steel products and fabricated piping systems. Personal breathing zone air sampling concentrations of chromium (VI) were above the NIOSH REL. The highest concentrations for nickel and chromium (VI) occurred during welding operations inside large stainless steel pipes (0.26 mg/m^3 and 0.36 mg/m^3), and while welding fins on a large stainless steel pipe (Hall *et al.*, 2005).

As part of an international epidemiological study of workers in the pulp and paper industry, Teschke *et al.* (1999) assembled and analysed 7293 previously unpublished exposure measurements collected in non-production departments from 147 mills in 11 countries. Chromium (VI) compounds were reported in 26 time-weighted average (TWA) samples from nine mills, with a mean airborne chromium (VI) concentration of 63 μg/m^3 (range, 0.04–1220 μg/m^3).

Proctor *et al.* (2003) analysed more than 800 measurements of airborne chromium (VI) from 23 surveys conducted during 1943–71 at a chromate production plant in Painesville, Ohio, USA. The highest chromium (VI) concentrations recorded at the plant occurred in shipping (e.g. bagging of dichromate), lime and ash, and filtering operations (maximum yearly TWA concentrations of 8.9, 2.7, and 2.3 mg/m^3, respectively). The data showed that concentrations in the indoor operating areas of the plant generally decreased over time, dropping from 0.72 mg/m^3 in the 1940s, to 0.27 mg/m^3 in 1957–64, and to 0.039 mg/m^3 in 1965–72.

In a study to assess industry compliance with existing and proposed standards, Lurie & Wolfe (2002) conducted a secondary data analysis of 813 chromium (VI) measurements collected in 1990–2000 by OSHA. Chromium (VI) was not detected in 436 measurements. In the remaining samples, the median 8-hour TWA concentration was 10 mg/m^3 (n = 197; range, 0.01–13960 mg/m^3), and the median ceiling concentration was 40.5 mg/m^3 (n = 180; range, 0.25–25000 mg/m^3). In the plating and polishing industry, the median 8-hour TWA concentration was 8.2 mg/m^3 (n = 65; range, 0.01–400 mg/m^3), and the median ceiling concentration was 23 mg/m^3 (n = 51; range, 1–410 mg/m^3).

Luippold *et al.* (2005) examined the mortality of two cohorts of chromate production workers constituting the current US chromium chemical industry, after engineering controls were implemented. Personal air monitoring sampling for chromium (VI) at the two plants resulted in approximately 5230 personal air-monitoring measurements taken during 1974–88 for Plant 1, and 1200 measurements taken during 1981–98 for Plant 2. Personal levels of chromium (VI) exposure were very low at both plants (geometric mean, < 1.5 μg/m^3 for most years; range of annual means, 0.36–4.36 μg/m^3). At both plants, the work areas with the highest average exposures were generally less than 10 μg/m^3 for most years.

In an occupational exposure study of chromium in an aircraft construction factory, personal airborne samples were collected in a group of 16 workers over a 4-hour period, and urinary samples were collected from 55

workers at the beginning of their work shift (on Monday), and at the beginning and end of their work shift (on Friday). The geometric mean air concentration was 0.17 μg/m^3 (GSD, 5.35 μg/m^3; range, 0.02–1.5 μg/m^3). Geometric mean creatinine levels were as follows: pre-shift Monday, 0.63 μg/g (GSD, 0.53 μg/g; range, 0.23–2.9 μg/g); pre-shift Friday, 0.95 μg/g (GSD, 0.94 μg/g; range, 0.25–4.8 μg/g); and post-shift Friday, 0.91 μg/g (GSD, 1.38 μg/g; range, 0.16–7.7 μg/g) (Gianello *et al.*, 1998).

2. Cancer in Humans

2.1 Introduction

A large number of case reports dating to the late 19th and early-to-mid-20th centuries raised suspicions that workers in various industries with exposure to chromium compounds, including chromate production, production of chromate pigments and chromium plating may be at risk of developing various cancers (Newman, 1890; Pfeil, 1935; Teleky, 1936; IARC, 1990). Beginning in the mid-20th century, cohort studies were undertaken in these industries as well as in some other occupations and industries with potential exposure to chromium compounds, such as ferrochromium or stainless steel production, welding, leather tanning, and some others. By the 1980s considerable evidence had accumulated on cancer risks of chromium-exposed workers, and leading to the identification of chromium (VI) compounds as a human carcinogen (IARC, 1990).

The strongest evidence presented at the time concerned the lung. There was weaker and less consistent evidence of effects on gastrointestinal sites, mainly stomach, and some reports of excess risks at several other organs, such as pancreas, prostate and bladder. Furthermore, there were some case reports and small clusters of nasal or sinonasal cavity cancers in workers exposed to chromium (VI). Based on the review of the previous *IARC Monograph*, and on a subsequent review of relevant epidemiological evidence accumulated since then, the Working Group focused the current review on those sites for which the evidence indicates possible associations with chromium (VI) compounds, namely: lung, nose, and nasal sinus. Because of recent controversy regarding possible effects on stomach cancer (Proctor *et al.*, 2002; Beaumont *et al.*, 2008), the Working Group also reviewed relevant evidence for this organ. For other organs, the number of reports of excess risks is unremarkable in the context of the numbers of studies that have been conducted, and thus they have not been reviewed.

There have been at least 50 epidemiological studies that could be informative about cancer risks related to chromium (VI). Many of the studies have given rise to multiple reports; sometimes these simply represent follow-up updates, but often the different reports also present different types of analyses of subgroups or of case–control analyses within a cohort. Only a minority of the studies contain documented measurements of chromium (VI) exposure, particularly measurements that pertain to the era of exposure of the workforce that was investigated. It was therefore necessary to select and present the evidence according to the availability of relevant exposure information. The studies were triaged into the following categories:

1. Cohort studies in industries in which workers were highly likely to have been exposed at relatively high levels. This included workers in chromate production, chromate pigment production, and chromium electroplating.
2. Cohort studies in which workers were possibly exposed to relatively high levels but not with the same degree of certainty or concentration as those in category a. This included stainless steel welders.
3. Other studies in which workers may have been exposed to chromium (VI), but with lower likelihood or lower frequency or lower

concentrations than workers in categories 1) and 2). Among the occupations/industries in this category were ferrochromium and stainless steel production, mild steel welding, general paint production, general spray painting, tanneries, gold mining, and nickel plating.

Studies in category 3) were not routinely included in the current review because there were sufficiently informative studies in categories 1) and 2), except if the authors presented information indicative of exposure to non-negligible levels of chromium (VI).

Most of the informative evidence comes from industry-based cohort studies, some of which have been complemented by nested case–control analyses. One of the main limitations of industry-based cohort studies is the usual absence of information on smoking and other potential confounders aside from age, sex, and race. Nonetheless, except for some case–control studies of nasal cancer, the Working Group relied on cohort studies to provide informative results.

For each study selected, the Working Group chose the most recent publication; occasionally there were results in earlier papers that were also deemed important to present here. Further, in each publication there are typically a large number of results presented by organ site, by demographic characteristics of workers, by some index of duration or dose of exposure, and sometimes by analysing the data in a nested case–control fashion. For the purposes of the current review, the Working Group selected the key results from each publication, typically including the most general result available for workers exposed to chromium (VI) as well as a result for a subgroup characterized by relatively high duration or dose of exposure, when there were enough numbers in such a category.

2.2 Cancer of the lung

Almost all of the relative risk estimates for cancer of the lung presented in Table 2.1 (available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-04-Table2.1.pdf) are greater than 1.0. Among chromate production workers, virtually all studies showed excess risks of lung cancer, except for a few estimates of risks for US workers hired since exposures were lowered (Luippold *et al.*, 2005), but these latter analyses had few subjects and low power.

Similarly, studies of chromate pigment production workers tended to show elevated risks of lung cancer in nearly all the cohorts and subcohorts reported, though not every relative risk estimate was statistically significant. Also, among chromium electroplating workers, there was a clear pattern of excess risks in most cohorts. Workers in other industries who may have had somewhat lower levels of chromium (VI) exposure than those in the previously mentioned industries, had a less convincing set of relative risk estimates, though nearly all were above 1.0.

A few of the cohort studies collected high-quality smoking histories, and incorporated these into nested case–control analyses; these tended to show elevated risks independent of smoking. Several other studies had collected partial or representative smoking frequencies among their workers, and for most of these studies, the main results were unlikely to have been meaningfully confounded by smoking patterns in the workers.

A recent meta-analysis estimated an overall standardized mortality ratio (SMR) of 1.41 (95%CI: 1.35–1.47) for lung cancer among 47 studies of workers with possible chromium (VI) exposure (Cole & Rodu, 2005). [The Working Group noted that because of the great difficulty in establishing equivalencies between different studies in terms of the types and levels of exposures to chromium (VI), the summary estimates are difficult to interpret. Further, it appears

that some of the study populations in that meta-analysis overlapped with each other.]

In aggregate, the results continue to show that exposure to chromium (VI) increases the risks of lung cancer.

Very few of the epidemiological studies provided results relating to specific chromium (VI) compounds. Workers in chromate production were likely to have been exposed to mixtures of sodium, potassium, calcium and ammonium chromates and dichromates; the highest and most consistent excess risks were observed in these cohorts. Workers in chromate pigment production and spray painting were likely to have been exposed to zinc and/or lead chromates, also resulting in high risks. Steel smelting and welding probably resulted in exposure to alkaline chromates, and risks reported in these cohorts tended to be less clear than among the chromate producers and the chromate pigment producers. Because there seemed to be increased risks in diverse industries involving exposure to a variety of chromium (VI) compounds of varying solubilities, this observation argues for a general carcinogenic effect of chromium (VI).

2.3 Cancer of the nose and nasal sinus

Cancer of the nose and nasal sinus is extremely rare, the incidence of which is roughly 1/100th of the incidence of cancer of the lung (Parkin *et al.*,1997). In fact, most cohorts of workers exposed to chromium (VI) do not report on of the incidence of nose and nasal sinus cancers. [The Working Group noted that this could mean there were none in the cohort or that the investigators did not examine and report it.]

Table 2.2 (available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-04-Table2.2.pdf) shows the nine (ten studies including Sorahan *et al.*, 1987) cohort studies that did report how many nasal cancers occurred. Combining those nine (ten) cohorts, there were mentions of 22 (25) cases of nasal or nasal sinus cancer. For the four cohorts that reported an expected as well as an observed number of cases, the aggregate was 12 observed and 1.5 expected giving an SMR of 8.0. Because several cohort studies failed to report any cases, it is difficult to integrate the appropriate observed and expected numbers from these studies into the overall estimate of risk from cohort studies. [The Working Group believed that many of the studies which made no report on nasal cancer actually had none.]

Case reports since the 1960s have reported 11 (12 including one case reported in Enterline, 1974) cases of nasal or nasal sinus cancer among chromate workers. Without any indication of person-years at risk, it is difficult to infer whether this represents an excess.

There have been three informative case–control studies on nasal and nasal sinus cancer. Two showed some indications of excess risk among workers with possible exposure to chromium (VI) compounds, but the study with the best exposure assessment protocol (Luce *et al.*, 1993) reported no excess risks for workers exposed to chromium (VI).

In aggregate, the epidemiological evidence remains suggestive but inconclusive regarding the effect of chromium (VI) on nasal and nasal sinus cancers. [The Working Group noted that systematic confounding by nickel exposure is unlikely in the cohorts presented in Table 2.2 online.]

2.4 Cancer of the stomach

There is little evidence of an association between exposure to chromium (VI) and cancer of the stomach; there are as many point estimates above 1.0 as there are below. There has been concern about possible hazards related to the ingestion of chromium (VI) in drinking-water, and one study in the People's Republic of China

(Zhang & Li, 1987) and a subsequent reanalysis of the Chinese data (Beaumont *et al.*, 2008) seem to indicate a somewhat elevated risk of stomach cancer in which drinking-water was heavily polluted by a ferrochromium plant. However, one single ecological study does not constitute rigorous evidence of an association between exposure to chromium (VI) and cancer of the stomach.

See Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-04-Table2.3.pdf.

2.5 Synthesis

The large majority of informative cohort studies indicate that there is an excess risk of lung cancer among workers exposed to chromium (VI), particularly in chromate production, chromate pigment production, and chromium electroplating. It is unlikely that any biases or chance can explain these findings.

There are some case reports, cohort studies and case–control studies that suggest a possible excess of cancer of the nose and nasal sinus among workers exposed to chromium (VI). However, this evidence is susceptible to publication and reporting biases because many of the cohort studies did not report on nasal cancers, and it is not clear how to evaluate the significance of the case reports.

There is little evidence that exposure to chromium (VI) causes stomach or other cancers.

3. Cancer in Experimental Animals

Chromium (VI) compounds have been tested for carcinogenicity by several routes in several animal species and strains (IARC, 1990), and the following paragraphs summarize some key findings from previous IARC evaluations of chromium (VI) compounds.

Calcium chromate induced lung tumours in mice (males and females combined) when given by inhalation (Nettesheim *et al.*, 1971) and local tumours when given by intramuscular administration (Payne, 1960). In rats it caused lung tumours (adenoma, squamous cell carcinoma, or adenocarcinoma) when given by intratracheal administration (Steinhoff *et al.*, 1986) or intrabronchial administration (Levy & Venitt, 1986), bronchial (carcinomas or squamous cell carcinomas) when administered by intrabronchial administration (Levy *et al.*, 1986), and local tumours in rats treated by intrapleural (Hueper, 1961; Hueper & Payne, 1962) or intramuscular administration (Hueper & Payne, 1959, 1962; Hueper, 1961; Roe & Carter, 1969).

Lead chromate (and its derived pigments), administered by subcutaneous injection (Maltoni, 1974, 1976; Maltoni *et al.*, 1982) or intramuscular injection cause malignant tumours at the site of injection and renal tumours (Furst *et al.*, 1976) in rats. Subcutaneous administration of basic lead chromate caused local sarcomas in rats (Maltoni, 1974, 1976; Maltoni *et al.*, 1982). In rats, zinc chromates caused bronchial carcinomas when administered by intrabronchial implantation (Levy *et al.*, 1986), and local tumours when given intrapleurally (Hueper, 1961), subcutaneously (Maltoni *et al.*, 1982) or intramuscularly (Hueper, 1961). Strontium chromate also caused bronchial carcinomas (intrabronchial implantation administration) (Levy *et al.*, 1986), and local sarcomas (intrapleural and intramuscular administration) in rats (Hueper, 1961).

Chromium trioxide when tested as a mist by inhalation caused nasal papillomas in mice (Adachi & Takemoto, 1987). Local tumours were observed in rats exposed to sintered chromium trioxide (Hueper & Payne, 1959). A low incidence of lung adenocarcinomas was induced after inhalation of chromium trioxide, and some lung tumours were observed in rats exposed by intrabronchial administration but neither were

statistically significant (Adachi *et al.*, 1986; Levy *et al.*, 1986; Levy & Venitt, 1986).

Sodium dichromate (when given by inhalation or intratracheal administration) caused lung tumours (benign and malignant) (Glaser *et al.*, 1986; Steinhoff *et al.*, 1986) in rats.

3.1 Studies published since the previous *IARC Monograph*

Since the previous *IARC Monograph* (IARC, 1990), studies in experimental animals have been conducted to evaluate oral exposure to chromium (VI). Table 3.1 summarizes the results of these studies, and the text below summarizes the major findings for each specific compound.

3.1.1 Sodium dichromate dihydrate

The National Toxicology Program (NTP) conducted 2-year drinking-water studies of sodium dichromate dihydrate in male and female B6C3F$_1$ mice, and in male and female F344 rats. In rats, sodium dichromate dihydrate significantly increased the incidence of squamous cell epithelium tumours of the oral mucosa or tongue in the high-dose groups (516 mg/L) of males and females. Trend analysis indicated a dose–response relationship in both males and females. In mice, sodium dichromate dihydrate significantly increased tumours (adenomas or carcinomas) of the small intestine (duodenum, jejunum, or ileum) in the two-highest dose groups of males (85.7 and 257.4 mg/L) and females (172 and 516 mg/L). Dose–response relationships were observed in both sexes (NTP, 2008).

3.1.2 Potassium chromate

Davidson *et al.* (2004) studied the effects of potassium chromate on ultraviolet(UV)-induced skin tumours in female hairless mice (CRL: SK1-hrBR). Mice were exposed to UV alone, various concentration of potassium chromate alone (given in the drinking-water), and UV together with various concentrations of potassium chromate. Administration of drinking-water containing potassium chromate did not induce skin tumours alone. However, chromate treatment significantly increased the multiplicity of UV-induced skin tumours, and the multiplicity of malignant UV-induced skin tumours. Similar results were found in male and female hairless mice (Uddin *et al.*, 2007). The analysis of skin indicated that UV treatment increased the level of chromium in the exposed skin (Davidson *et al.*, 2004).

3.2 Synthesis

The administration of calcium chromate in mice and sodium dichromate in rats by inhalation caused lung cancer. Calcium chromate and sodium dichromate administered by intratracheal instillation caused lung cancer in rats. Intratracheal administration of calcium chromate, zinc chromate, and strontium chromate caused lung cancer in rats. Several chromium compounds by repository injection (calcium chromate, lead chromate, zinc chromate, strontium chromate) caused local sarcomas. Oral administration of sodium dichromate to rats and mice caused cancer of the oral cavity and of the gastrointestinal tract. Potassium chromate given orally, although not given alone, enhanced UV-induced skin carcinogenesis, indicating tumour systemic effects.

Table 3.1 Studies of cancer in experimental animals exposed to chromium (VI) (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance[a]	Comments
Sodium dichromate dihydrate				
Rat, F344/N (M, F) 2 yr NTP (2008)	Drinking-water 0, 14.3, 57.3 172, 516 mg/L Average daily doses: M-0, 0.6, 2.2 6, 17 mg/kg bw F-0, 0.7, 2.7, 7, 20 mg/kg bw *ad libitum* 50/group/sex	Oral mucosa (squamous cell carcinomas):[b] M–0/50, 0/50, 0/49, 0/50, 6/49 (12%) F–0/50, 0/50, 0/50, 2/50 (4%), 11/50 (22%) Tongue (squamous cell papillomas or carcinomas): M–0, 1, 0, 0, 1 F–1, 1, 0, 1, 0 Oral mucosa or tongue:[c] M–0/50, 1/50 (2%), 0/49, 0/50, 7/49 (14%) F–1/50 (2%), 1/50 (2%), 0/50, 2/50 (4%), 11/50 (22%)	M: $P < 0.05$ (high dose); $P_{trend} < 0.001$ F: $P < 0.001$ (high dose); $P_{trend} < 0.001$ M: $P < 0.01$; $P_{trend} < 0.001$ F: $P < 0.01$ (high dose); $P_{trend} < 0.001$	Age at start, 6–7 wk 99.7% pure No treatment effects on survival Decreased bw in high-dose males and females Decreased water consumption of the 2 highest doses
Mouse, B6C3F$_1$ (M, F) 2 yr NTP(2008)	Drinking-water M: 0, 14.3, 28.6, 85.7, 257.4 mg/L F: 0, 14.3, 57.3, 172, 516 mg/L Average daily doses: M–0, 1.1, 2.6, 7, 17 mg/kg bw F–0, 1.1, 39.9, 9, 25 mg/kg bw *ad libitum* 50/group/sex	Small intestine (adenomas): M–1/50 (2%), 1/50 (2%), 1/50 (2%), 5/50 (10%), 17/50 (34%) F–0/50, 1/50 (2%), 2/50 (4%), 15/50 (30%), 16/50 (32%) Small intestine (carcinomas): M–0/50, 2/50 (4%), 1/50 (2%), 3/50 (6%), 5/50 (10%) F–1/50 (2%), 0/50, 2/50 (4%), 3/50 (6%), 7/50 (14%) Small intestine (adenomas or carcinomas):[d] M–1/50 (2%), 3/50 (6%), 2/50 (4%), 7/50 (14%), 20/50 (40%) F–1/50 (2%), 1/50 (2%), 4/50 (8%), 17/50 (34%), 22/50 (44%)	M: $P < 0.001$ (high dose); $P_{trend} < 0.001$ F: $P < 0.001$ (2 highest doses); $P_{trend} < 0.001$ M: $P < 0.05$ (high dose); $P_{trend} < 0.05$ F: $P < 0.05$ (high dose); $P_{trend} < 0.001$ M: $P < 0.001$ (high dose), $P < 0.05$ (85.7 mg/L), $P_{trend} < 0.001$ F: $P < 0.001$ (2 highest doses 172 and 516 mg); $P_{trend} < 0.001$	Age at start, 6–7 wk 99.7% pure No treatment effects on survival Decreased body weight in 2 highest female dose groups Decreased water consumption of the 2 highest doses (males and females) Most of the tumours were located in the duodenum

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance[a]	Comments
Potassium chromate (K_2CrO_4)				
Mouse, CRL: Sk1-hrBR (F) 224 d Davidson *et al.* (2004)	Group 1: Controls Group 2: UV only Group 3: 2.5 ppm K_2CrO_4 Group 4: 5 ppm K_2CrO_4 Group 5: UV +0.5 ppm K_2CrO_4 Group 6: UV + 2.5 ppm K_2CrO_4 Group 7: UV + 5 ppm K_2CrO_4: UV: 1 mo after K_2CrO_4 1.1 kJ/m^2 3 d/wk for 3 mo, followed by 1 wk break, and 1.3 kJ/m^2, 2 d/wk for 3 mo K_2CrO_4: 182 d, added to drinking-water every 7–10 d 120 animals	Skin (tumours): Groups 1, 3, 4–no tumours *Number of tumours (> 2mm/no of mice at 182 d):* Group 2–12/15 (0.8) Group 5–16/12 (1.39) Group 6–50/19 (2.63) Group 7–94/19 (5.02)	Group 6 vs Group 2, $P < 0.05$ Group 7 vs Group 2, $P < 0.01$	Age at start, 6 wk Chromium-only treatment had no effects on bw or toxicity Levels of chromium were measured in dorsal thoracic skin and abdominal skin in Groups 1, 4, and 7 UV + chromium had significantly higher chromium levels in back and underbelly skin

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance[a]	Comments
Mouse, CRL: Sk1-hrBR (M, F) 224 d Uddin *et al.* (2007)	Groups: treatment, *n* Group 1a: UV, 10 Group 1a: UV + 2.5 ppm K_2CrO_4, 10 Group 1c: UV + 5 ppm K_2CrO_4, 10 Group 2a: UV + 5 ppm K_2CrO_4, 10 Group 2b: UV + 5 ppm K_2CrO_4 + Vitamin E, 10 Group 2c: UV + 5 ppm K_2CrO_4 + selenium, 10 Mice administered K_2CrO_4 in drinking-water at 3 wk of age. 3 wk later UV treatment (1.0 kJ/m^2) 3 d/wk for 26 wk Vitamin E: 62.5 IU/kg Selenium: 5 mg/kg Group 1–males, Group 2–females (30/group)	Skin (number of tumours/mice at 26 wk): M– Group 1a: 1.9 ± 0.4 Group 1b: 5.9 ± 0.8 Group 1c: 8.6 ± 0.9 F– Group 2a: 3.9 ± 0.6 Group 2b: 3.5 ± 0.6 Group 2c: 3.6 ± 0.6	Group 1b vs 1a, $P < 0.001$ Group 1c vs 1a, $P < 0.0001$	Age, 3 wk Chromium had no effect on growth of the mice. Chromium levels in skin increased with dose Chromium also decreased the time until appearance of first tumours in males

[a] *P*-values for calculated by Poly 3- for NTP studies, which accounts for differential mortality in animals that do not reach terminal sacrifice.
[b] Historical control incidence for 2-yr drinking-water studies with NTP-20000 diet: M: 0/300, F: 0/300.
[c] Historical control incidence for 2-yr drinking-water studies with NTP-20000 diet: M: 2/300, range 0 to 2%; F: 3/300, range 0 to 2%.
[d] Historical control incidence for 2-yr drinking-water studies with NTP-20000 diet: M:11/299, range 0–10%; F: 4/350, range 0 to 4%.
[e] Borneff *et al.* (1968) published in German.
[f] No information on tumour incidence of this group was reported by Sedman *et al.* (2006).
[g] Two-Tailed Fisher Exact Test; Authors stated significant but did not provide*P*-value.
[h] Untreated and chromium only, controls not included since no tumours were observed in the study by Davidson *et al.* (2004).
bw, body weight; d, day or days; F, female; M, male; mo, month or months; UV, ultraviolet; vs, versus; wk, week or weeks; yr, year or years

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

In humans, the absorption, retention, and elimination of chromium compounds after exposure by inhalation depend on the solubility and particle size of the particular compound inhaled (for an extensive review, see ATSDR, 2008b). The retention may range from several hours to weeks. Inhaled chromium (VI) is readily absorbed from the respiratory tract. The degree of absorption depends on the physical and chemical properties of the particles (size, solubility), and the extent of reduction of the hexavalent form to chromium (III), which is absorbed to a much lesser extent. Thus, after intratracheal instillation in rats, 53–85% of chromium (VI) compounds with a particle size < 5 µm are absorbed into the bloodstream, with higher absorption rates in case of more soluble compounds; the rest remains in the lungs. For comparison, absorption of chromium (III) from the respiratory tract is only 5–30% (ATSDR, 2008b). The same factors mentioned above apply to absorption from the gastrointestinal tract, although absorption by this route is generally much less compared with that in the respiratory tract. Average absorption fractions determined in human volunteers for chromium (III) or chromium (VI) were reported as 0.13% or 6.9%, respectively. Chromium (VI) can penetrate human skin to some extent (ATSDR, 2008b).

In humans and rodents, absorbed chromium (VI) is distributed in nearly all tissues, with the highest concentrations found in the kidney, liver, and bone. Studies conducted by the NTP in male rats and female mice orally exposed to chromium (VI) for 2 years showed dose-related and time-dependent increases in total chromium concentrations in red cells, plasma, and in several organs. The total chromium content of the red cells was higher than that of plasma. The concentration of total chromium in the forestomach was found to be markedly higher in mice than in rats (NTP, 2008).

Within the human body, chromium (VI) undergoes a series of reduction steps to form the thermodynamically stable chromium (III). When reduction occurs extracellularly, this process can be considered as detoxification because the cell membrane is a nearly impermeable barrier for chromium (III). The remaining chromium (VI) is present as a mixture of chromate (CrO_4^{2-}) and hydrochromate ($HCrO_4^-$); because water-soluble chromates are iso-structural with sulfate and phosphate ions, they are readily taken up by sulfate channels. In case of poorly water-soluble chromates, particles of < 5 µm can be phagocytosed, and gradually dissolved intracellularly. Within the cell, chromium (VI) is reduced stepwise to chromium (III), giving rise to reactive intermediates as well as DNA and protein adducts. In blood, chromium (VI) is taken up into red blood cells, is reduced, and then bound to proteins. After exposure by inhalation, excretion occurs predominantly via the urine. Due to the low absorption of chromium compounds from the gastrointestinal tract, the major pathway of elimination after oral exposure is through the faeces (ATSDR, 2008b).

4.2 Genetic and related effects

The oxidation state of chromium is the most important factor when considering its biochemical activity (Beyersmann & Hartwig, 2008; Salnikow & Zhitkovich, 2008). Chromium (VI), but not chromium (III) compounds, have been shown to exert genotoxicity both *in vivo* and *in vitro*.

Lymphocytes of workers exposed to dusts of chromium (VI) compounds showed elevated frequencies of DNA strand breaks (Gambelunghe *et al.*, 2003), sister chromatid exchange (Wu *et al.*, 2001), and micronuclei (Vaglenov *et al.*, 1999; Benova *et al.*, 2002).

After intratracheal instillation in rats, chromium (VI) induced DNA strand breaks in lymphocytes (Gao *et al.*, 1992). After intraperitoneal injection of chromium (VI) to mice, micronuclei were induced in bone marrow. In contrast, no micronucleus induction was observed after oral administration, indicating that chromium (VI) does not reach the target cells to a high extent by this route of exposure (De Flora *et al.*, 2006). Chromium (VI) induces dominant lethal mutations in male mice (Paschin *et al.*, 1982).

In vitro, soluble chromium (VI) compounds are mutagenic in mammalian and bacterial test systems (De Flora *et al.*, 1990).

4.2.1 DNA damage

Chromium (VI) is unreactive towards DNA under physiological conditions. According to the uptake–reduction model originally established by Wetterhahn *et al.* (1989), chromium (VI) undergoes a series of reduction steps in cells, to form the thermodynamically stable chromium (III). Intracellular reduction does not require enzymatic steps but is mediated by direct electron transfer from ascorbate and non-protein thiols, such as glutathione and cysteine. During the reduction process, variable amounts of chromium (V) and chromium (IV) as well as organic radical species are generated; their exact nature, however, depends largely on the reducing species (Wetterhahn & Hamilton, 1989). Furthermore, comparative in-vivo and in-vitro studies revealed a major impact of the intracellular reductants on the nature and biological consequences of the resultant DNA lesions.

The major intracellular reductant under physiological conditions appears to be ascorbate, reaching millimolar concentrations in human tissues, and accounting for about 90% of chromium (VI) reduction reactions *in vivo* (Standeven *et al.*, 1992). In contrast, only micromolar concentrations of ascorbate are usually present in cell cultures (Quievryn *et al.*, 2002), which leads to an increase in thiol-mediated chromate reduction. When ascorbate is the reductant, two electrons are transferred, and chromium (IV) but not chromium (V) is generated as the first intermediate, whereas with cysteine as a reductant, predominantly chromium (V) is formed due to one-electron transfers (Stearns & Wetterhahn, 1994). In both cases, the final product is chromium (III), which reacts to produce different types of DNA lesions.

DNA lesions generated after exposure to chromium (VI) include chromium (III)–DNA adducts, DNA–protein and DNA–DNA interstrand crosslinks, DNA breaks as well as several oxidative DNA–base modifications. The predominant form of chromium (III)–DNA adducts are ternary adducts, where chromium forms a link between DNA and small molecules such as cysteine, histidine, glutathione or ascorbate, presumably arising from preformed chromium–ligand complexes during the reduction process. These adducts are formed primarily at phosphate groups, but the subsequent partial formation of chelates involving the phosphate group and the N^7-position of guanine have been suggested. Chelates formed from chromium–ascorbate particularly are potent premutagenic DNA lesions (Zhitkovich *et al.*, 2001).

The formation of DNA–protein crosslinks after chromate exposure is well established, but is estimated to account for less than 1% of chromium–DNA adducts. Biological consequences are likely to be disturbances of DNA replication and transcription. The formation of DNA–DNA crosslinks appears to be restricted to certain in-vitro conditions, due to severe steric hindrance upon intercalation of octahedral chromium (III) complexes (Zhitkovich, 2005).

DNA single-strand breaks may arise due to the reaction of chromium (V) with hydrogen peroxide, forming hydroxyl radicals. Nevertheless, if ascorbate is the predominant reductant under in-vivo conditions, the generation of chromium (V) and thus, single-strand

breaks, appears to be of minor importance (Quievryn *et al.*, 2003). Cytogenetic alterations in chromium (VI)-exposed cells in culture and *in vivo*, such as increased frequencies of chromosomal breaks and micronuclei, are suggested to be due to DNA double-strand breaks, produced by a cell-replication-dependent mechanism in the G2 phase of the cell cycle. Recent evidence suggests the involvement of mismatch repair in the formation of double-strand breaks. Thus, highly mutagenic ascorbate–chromium–DNA adducts lead to the error-prone repair of double-strand breaks through non-homologous end-joining. Furthermore, they induce mismatches during replication, leading to aberrant mismatch repair. Based on these findings, a model has been created to show that chronic exposure to toxic doses of chromium (VI) provokes the selective outgrowth of mismatch-repair-deficient clones with high rates of spontaneous mutagenesis, and thus, genomic instability (Reynolds *et al.*, 2007; Salnikow & Zhitkovich, 2008). In support of this model, chromium-induced cancers in exposed workers were associated with microsatellite instability and exhibited the loss of expression of MLH1, which is one of the essential mismatch-repair proteins (Takahashi *et al.*, 2005).

4.2.2 Oxidative stress

In the reduction of chromium (VI) to chromium (III) by cellular reductants, potentially toxic intermediates (oxygen radicals, sulfur radicals, and chromium radicals) are generated (Yao *et al.*, 2008). In a cell-free system, chromium (VI) reacted with glutathione to form chromium (V) and thiyl radicals (Wetterhahn *et al.*, 1989). Furthermore, after reduction of chromium (VI) by glutathione, chromium (V) can undergo Fenton-type reactions, producing hydroxyl radicals (Shi *et al.*, 1994), and 8-oxoguanine in isolated DNA (Faux *et al.*, 1992). In cultured mammalian cells, chromium (VI) induced the formation of superoxide and nitric oxide (Hassoun & Stohs, 1995). The administration of chromium (VI) to animals, which have higher tissue levels of ascorbate compared with cultured cells, did not induce the formation of 8-oxoguanine (Yuann *et al.*, 1999). This may be due to the lack of chromium (V) formation when ascorbate is the predominant reducing agent.

4.2.3 Further potentially relevant mechanisms

Besides direct genotoxic effects of chromium (VI) metabolites, chromate may activate various mitogen-activated protein kinases as well as transcription factors involved in inflammation and tumour growth. Nevertheless, because these effects have been observed in cell-culture systems and no distinct effects of chromium (VI) on cell proliferation have been shown, the relevance of these observations remains unclear at present. Perhaps of higher impact are the aneugenic properties of chromium (VI). Chronic treatment with lead-chromate particles induced neoplastic transformation of human bronchial cells, which was accompanied by centrosome amplification, and an increase in aneuploid metaphases (Xie *et al.*, 2007).

4.3 Synthesis

Several mechanisms are involved in the carcinogenesis induced by chromium (VI) that include the induction of DNA damage, the generation of oxidative stress and aneuploidy, leading to cell transformation. With respect to DNA damage, the spectrum of induced lesions appears to depend strongly on the cellular reductant involved. Thus, under physiological conditions with ascorbate as the major reductant, the generation of premutagenic ternary chromium–ascorbate–DNA adducts appears to be of major relevance, which may be linked to the increased number of mismatch-repair-resistant cells observed in chromate-induced lung tumours.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of chromium (VI) compounds. Chromium (VI) compounds cause cancer of the lung. Also positive associations have been observed between exposure to Chromium (VI) compounds and cancer of the nose and nasal sinuses.

There is *sufficient evidence* in experimental animals for the carcinogenicity of chromium (VI) compounds.

Chromium (VI) compounds are *carcinogenic to humans (Group 1).*

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NICKEL AND NICKEL COMPOUNDS

Nickel and nickel compounds were considered by previous IARC Working Groups in 1972, 1975, 1979, 1982, 1987, and 1989 (IARC, 1973, 1976, 1979, 1982, 1987, 1990). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms, trade names, and molecular formulae for nickel, nickel alloys, and selected nickel compounds are presented in Table 1.1. This list is not exhaustive, nor does it necessarily reflect the commercial importance of the various nickel-containing substances, but it is indicative of the range of nickel alloys and compounds available, including some compounds that are important commercially, and those that have been tested in biological systems. Several intermediary compounds occur in refineries that cannot be characterized, and are thus not listed.

1.2 Chemical and physical properties of the agents

Nickel (atomic number, 28; atomic weight, 58.69) is a metal, which belongs to group VIIIB of the periodic table. The most important oxidation state of nickel is +2, although the +3 and +4 oxidation states are also known (Tundermann *et al.*, 2005). Nickel resembles iron, cobalt, and copper in its chemical properties. However, unlike cobalt and iron, it is normally only stable in aqueous solution in the + 2 oxidation state (Kerfoot, 2002). Selected chemical and physical properties for nickel and nickel compounds, including solubility data, were presented in the previous *IARC Monograph* (IARC, 1990), and have been reported elsewhere (ATSDR, 2005).

1.3 Use of the agents

The chemical properties of nickel (i.e. hardness, high melting point, ductility, malleability, somewhat ferromagnetic, fair conductor of heat and electricity) make it suitable to be combined with other elements to form many alloys (NTP, 2000; Tundermann *et al.*, 2005). It imparts such desirable properties as corrosion resistance, heat resistance, hardness, and strength.

Nickel salts are used in electroplating, ceramics, pigments, and as intermediates (e.g. catalysts, formation of other nickel compounds). Sinter nickel oxide is used in nickel catalysts in the ceramics industry, in the manufacture of alloy steel and stainless steel, in the manufacture of nickel salts for specialty ceramics, and in the manufacture of nickel–cadmium (Ni–Cd) batteries, and nickel–metal-hydride batteries. Nickel sulfide is used as a catalyst in

Table 1.1 Chemical names (CAS names are given in italics), synonyms, and molecular formulae or compositions of nickel, nickel alloys and selected nickel compounds

Chemical name	CAS Reg. No.	Synonyms	Formula
Metallic nickel and nickel alloys			
Nickel	7440-02-0	C.I. 77775; Nickel element	Ni
Ferronickel	11133-76-9	*Iron alloy (base), Fe, Ni*; nickel alloy (nonbase) Fe, Ni	Fe, Ni
Nickel aluminium alloys	61431-86-5 37187-84-1	*Raney nickel*; Raney alloy	NiAl
Nickel oxides and hydroxides			
Nickel hydroxide (amorphous)	12054-48-7 (11113-74-9)	Nickel dihydroxide; nickel (II) hydroxide; nickel (2+) hydroxide; *nickel hydroxide (Ni(OH)2)*; nickelous hydroxide	$Ni(OH)_2$
Nickel monoxide	1313-99-1 11099-02-8 34492-97-2	Black nickel oxide[a]; green nickel oxide; mononickel oxide; nickel monooxide; nickelous oxide; *nickel oxide (NiO)*; nickel (II) oxide; nickel (2+) oxide *Bunsenite (NiO)*	NiO
Nickel trioxide	1314-06-3	Black nickel oxide*d*; dinickel trioxide; nickelic oxide; nickel oxide; nickel (III) oxide; *nickel oxide (Ni_2O_3)*; nickel peroxide; nickel sesquioxide	Ni_2O_3
Nickel sulfides			
Nickel disulfide	12035-51-7 12035-50-6	*Nickel sulfide (NiS_2)* *Vaesite (NiS_2)*	NiS_2
Nickel sulfide (amorphous)	16812-54-7 (11113-75-0) 1314-04-1 (61026-96-8)	Mononickel monosulfide; nickel mono-sulfide; nickel monosulfide (NiS); nickelous sulfide; nickel (II) sulfide; nickel (2+) sulfide; *Nickel sulfide (NiS)* *Millerite (NiS)*	NiS
Nickel subsulfide	12035-72-2 12035-71-1	Nickel sesquisulfide; nickel subsulfide (Ni_3S_2); *nickel sulfide (Ni_3S_2)*; trinickel disulfide *Heazlewoodite (Ni_3S_2)*; Khizlevudite	Ni_3S_2
Pentlandite	53809-86-2 12174-14-0	Pentlandite ($Fe_9Ni_9S_{16}$) Pentlandite	Fe9Ni9S16 $(Fe_{0.4-0.6}Ni_{0.4-0.6})_9S_8$

Table 1.1 (continued)

Chemical name	CAS Reg. No.	Synonyms	Formula
Nickel salts			
Nickel carbonate	3333-67-3	*Carbonic acid, nickel (2+) salt (1:1)*; nickel carbonate (1:1); nickel (II) carbonate; nickel (2+) carbonate; nickel carbonate ($NiCO_3$); nickel (2+) carbonate ($NiCO_3$); nickel monocarbonate; nickelous carbonate	$NiCO_3$
Basic nickel carbonates	12607-70-4	Carbonic acid, nickel salt, basic; nickel carbonate hydroxide ($Ni_3(CO_3)(OH)_4$); *nickel, (carbonato(2-)) tetrahydroxytri-*	$NiCO_3.2Ni(OH)_2$
	12122-15-5	*Nickel bis(carbonato(2-)) hexahydroxypenta-*; nickel hydroxycarbonate	$2NiCO_3.3Ni(OH)_2$
Nickel acetate	373-02-4	*Acetic acid, nickel (2+) salt*; nickel (II) acetate; nickel (2+) acetate; nickel diacetate; nickelous acetate	$Ni(OCOCH_3)_2$
Nickel acetate tetrahydrate	6018-89-9	*Acetic acid, nickel (+2) salt, tetrahydrate*	$Ni(OCOCH_3)_2.4H_2O$
Nickel ammonium sulfates	15-699-18-0	Ammonium nickel sulfate ($(NH_4)_2Ni(SO_4)_2$); nickel ammonium sulfate ($Ni(NH_4)_2(SO_4)_2$); *sulfuric acid, ammonium nickel (2+) salt (2:2:1)*	$Ni(NH_4)_2(SO_4)_2$
Nickel ammonium sulfate hexahydrate	25749-08-0	Ammonium nickel sulfate ($(NH_4)_2Ni_2(SO_4)_3$); *sulfuric acid, ammonium nickel (2+) salt (3:2:2)*	$Ni_2(NH_4)_2(SO_4)_3$
	7785-20-8	Ammonium nickel (2+) sulfate hexahydrate; ammonium nickel sulfate ($(NH_4)_2Ni(SO_4)_2$); diammonium nickel disulfate hexahydrate; diammonium nickel (2+) disulfate hexahydrate; nickel ammonium sulfate ($Ni(NH_4)_2(SO_4)_2$) hexahydrate; nickel diammonium disulfate hexahydrate; *sulfuric acid, ammonium nickel (2+) salt (2:2:1), hexahydrate*	$Ni(NH_4)_2(SO_4)_2.6H_2O$
Nickel chromate	14721-18-7	*Chromium nickel oxide ($NiCrO_4$)*; nickel chromate ($NiCrO_4$); nickel chromium oxide ($NiCrO_4$)	$NiCrO_4$
Nickel chloride	7718-54-9	Nickel (II) chloride; nickel (2+) chloride; *nickel chloride ($NiCl_2$)*; nickel dichloride; nickel dichloride ($NiCl_2$); nickelous cholride	$NiCl_2$
Nickel chloride hexahydrate	7791-20-0	*Nickel chloride (NiCl2) hexahydrate*	$NiCl_2.6H_2O$
Nickel nitrate hexahydrate	13478-00-7	Nickel (2+) bis(nitrate)hexahydrate; nickel dinitrate hexahydrate; nickel (II) nitrate hexahydrate; nickel nitrate (Ni(NO3)2) hexahydrate; nickelous nitrate hexahydrate; *nitric acid, nickel (2+) salt, hexahydrate*	$Ni(NO_3)_2.6H_2O$
Nickel sulfate	7786-81-4	Nickel monosulfate; nickelous sulfate; nickel sulfate (1:1); nickel (II) sulfate; nickel (2+) sulfate; nickel (2+) sulfate (1:1); nickel sulfate ($NiSO_4$); *sulfuric acid, nickel (2+) salt (1:1)*	$NiSO_4$
Nickel sulfate hexahydrate	10101-97-0	*Sulfuric acid, nickel (2+) salt (1:1), hexahydrate*	$NiSO_4.6H_2O$
Nickel sulfate heptahydrate	10101-98-1	*Sulfuric acid, nickel (2+) salt (1:1), heptahydrate*	$NiSO_4.7H_20$

Table 1.1 (continued)

Chemical name	CAS Reg. No.	Synonyms	Formula
Other nickel compounds			
Nickel carbonyl	13463-39-3	*Nickel carbonyl ($Ni(CO)_4$), (T-4)-*; nickel tetracarbonyl; tetracarbonylnickel; tetracarbonylnickel (0)	$Ni(CO)_4$
Nickel antimonide	12035-52-8	*Antimony compound with nickel (1:1)*; nickel antimonide (NiSb); nickel compound with antimony (1:1); nickel monoantimonide	NiSb
	12125-61-0	*Breithauptite (SbNi)*	
Nickel arsenides	27016-75-7	*Nickel arsenide (NiAs)*	NiAs
	1303-13-5	Nickeline; *nickeline (NiAs)*; niccolite	NiAs
	12256-33-6	*Nickel arsenide ($Ni_{11}As_8$)*; nickel arsenide tetragonal	$Ni_{11}As_8$
	12044-65-4	*Maucherite ($Ni_{11}As_8$)*; Placodine; Temiskamite	$Ni_{11}As_8$
	12255-80-0	*Nickel arsenide (Ni_5As_2)*; nickel arsenide hexagonal	Ni_5As_2
Nickel selenide	1314-05-2 12201-85-3	Nickel monoselenide; *nickel selenide (NiSe)* Maekinenite; *Makinenite (NiSe)*	NiSe
Nickel subselenide	12137-13-2	*Nickel selenide (Ni_3Se_2)*	Ni_3Se_2
Nickel sulfarsenide	12255-10-6 12255-11-7	*Nickel arsenide sulfide (NiAsS)* *Gersdorffite (NiAsS)*	NiAsS
Nickel telluride	12142-88-0 24270-51-7	Nickel monotelluride; *nickel telluride (NiTe)* *Imgreite (NiTe)*	NiTe
Nickel titanate	12035-39-1	Nickel titanate(IV); nickel titanate (Ni-TiO3); *nickel titanium oxide (NiTiO3)*; nickel titanium trioxide	$NiTiO_3$
Chrome iron nickel black spinel	71631-15-7	CI: 77 504; *CI Pigment Black 30*; nickel iron chromite black spinel	$(Ni,Fe)(CrFe)_2O_4$ NS
Nickel ferrite brown spinel	68187-10-0	*CI Pigment Brown 34*	$NiFe_2O_4$
Nickelocene	1271-28-9	Bis(η5-2,4-cyclopentadien-1-yl)nickel; di-π-cyclopentadienylnickel; dicyclopentadienyl-nickel; bis(η5-2,4-cyclopentadien-1-yl)-nickel	π-(C5H5)2Ni

[a] In commercial usage, 'black nickel oxide' usually refers to the low-temperature crystalline form of nickel monoxide, but nickel trioxide (Ni_2O_3), an unstable oxide of nickel, may also be called 'black nickel oxide'.

the petrochemical industry or as an intermediate in the metallurgical industry.

According to the US Geological Survey, world use of primary nickel in 2006 was 1.40 million tonnes, a 12% increase over 2005. Stainless steel manufacture accounted for more than 60% of primary nickel consumption in 2006 (USGS, 2008). Of the 231000 tonnes of primary nickel consumed in the USA in 2007, approximately 52% was used in stainless and alloy steel production, 34% in non-ferrous alloys and superalloys, 10% in electroplating, and 4% in other uses. End uses of nickel in the USA in 2007 were as follows: transportation, 30%; chemical industry, 15%; electrical equipment, 10%; construction, 9%; fabricated metal products, 8%; household appliances, 8%; petroleum industry, 7%; machinery, 6%; and others, 7% (Kuck, 2008).

1.3.1 Metallic nickel and nickel alloys

Pure nickel metal is used to prepare nickel alloys (including steels). It is used as such for plating, electroforming, coinage, electrical components, tanks, catalysts, battery plates, sintered components, magnets, and welding rods. Ferronickel is used to prepare steels. Stainless and heat-resistant steels accounted for 93% of its end-use in 1986. Nickel-containing steels with low nickel content (< 5%) are used in construction and tool fabrication. Stainless steels are used in general engineering equipment, chemical equipment, domestic applications, hospital equipment, food processing, architectural panels and fasteners, pollution-control equipment, cryogenic uses, automotive parts, and engine components (IARC, 1990).

Nickel alloys are often divided into categories depending on the primary metal with which they are alloyed (e.g. iron, copper, molybdenum, chromium) and their nickel content. Nickel is alloyed with iron to produce alloy steels (containing 0.3–5% nickel), stainless steels (containing as much as 25–30% nickel, although 8–10% nickel is more typical), and cast irons. Nickel–copper alloys (e.g. Monel alloys) are used for coinage (25% nickel, 75% copper), industrial plumbing (e.g. piping and valves), marine equipment, petrochemical equipment, heat exchangers, condenser tubes, pumps, electrodes for welding, architectural trim, thermocouples, desalination plants, ship propellers, etc. Nickel–chromium alloys (e.g. Nichrome) are used in many applications that require resistance to high temperatures such as heating elements, furnaces, jet engine parts, and reaction vessels. Molybdenum-containing nickel alloys and nickel–iron–chromium alloys (e.g. Inconel) provide strength and corrosion resistance over a wide temperature range, and are used in nuclear and fossil-fuel steam generators, food-processing equipment, and chemical-processing and heat-treating equipment. Hastelloy alloys (which contain nickel, chromium, iron, and molybdenum) provide oxidation and corrosion resistance for use with acids and salts. Nickel-based super-alloys provide high-temperature strength and creep, and stress resistance for use in gas-turbine engines (ATSDR, 2005).

Other groups of nickel alloys are used according to their specific properties for acid-resistant equipment, heating elements for furnaces, low-expansion alloys, cryogenic uses, storage of liquefied gases, high-magnetic-permeability alloys, and surgical implant prostheses.

1.3.2 Nickel oxides and hydroxides

The nickel oxide sinters are used in the manufacture of alloy steels and stainless steels.

Green nickel oxide is a finely divided, relatively pure form of nickel monoxide, produced by firing a mixture of nickel powder and water in air at 1000 °C (IARC, 1990). It is used to manufacture nickel catalysts and specialty ceramics (for porcelain enamelling of steel; in the manufacture of magnetic nickel-zinc ferrites used in electric motors, antennas and television tube yokes; and

as a colourant in glass and ceramic stains used in ceramic tiles, dishes, pottery, and sanitary ware).

Black nickel oxide is a finely divided, pure nickel monoxide, produced by calcination of nickel hydroxycarbonate or nickel nitrate at 600 °C; nickel trioxide (Ni_2O_3), an unstable oxide of nickel, may also be called 'black nickel oxide' (IARC, 1990). Black nickel oxide is used in the manufacture of nickel salts, specialty ceramics, and nickel catalysts (e.g. to enhance the activity of three-way catalysts containing rhodium, platinum, and palladium used in automobile exhaust control).

Nickel hydroxide is used as a catalyst intermediate, and in the manufacture of Ni–Cd batteries (Antonsen & Meshri, 2005).

1.3.3 Nickel sulfides

Nickel sulfide is used as a catalyst in petrochemical hydrogenation when high concentrations of sulfur are present in the distillates. The major use of nickel monosulfide is as an intermediate in the hydrometallurgical processing of silicate-oxide nickel ores (IARC, 1990). Nickel subsulfide is used as an intermediate in the primary nickel industry (ATSDR, 2005).

1.3.4 Nickel salts

Nickel acetate is used in electroplating, as an intermediate (e.g. as catalysts and in the formation of other nickel compounds), as a dye mordant, and as a sealer for anodized aluminium.

Nickel carbonate is used in the manufacture of nickel catalysts, pigments, and other nickel compounds (e.g. nickel oxide, nickel powder); in the preparation of coloured glass; and, as a neutralizing compound in nickel-electroplating solutions.

Nickel ammonium sulfate is used as a dye mordant, in metal-finishing compositions, and as an electrolyte for electroplating.

Nickel chloride is used as an intermediate in the manufacture of nickel catalysts, and to absorb ammonia in industrial gas masks.

Nickel nitrate hexahydrate is used as an intermediate in the manufacture of nickel catalysts and Ni–Cd batteries.

Nickel sulfate hexahydrate is used in nickel electroplating and nickel electrorefining, in 'electroless' nickel plating, and as an intermediate (in the manufacture of other nickel chemicals and catalysts) (Antonsen & Meshri, 2005).

1.3.5 Other nickel compounds

The primary use for nickel carbonyl is as an intermediate (in the production of highly pure nickel), as a catalyst in chemical synthesis, as a reactant in carbonylation reactions, in the vapour-plating of nickel, and in the fabrication of nickel and nickel alloy components and shapes.

Nickelocene is used as a catalyst and complexing agent, and nickel titanate is used as a pigment (Antonsen & Meshri, 2005).

No information was available to the Working Group on the use of nickel selenides or potassium nickelocyanate.

1.4 Environmental occurrence

Nickel and its compounds are naturally present in the earth's crust, and are emitted to the atmosphere via natural sources (such as windblown dust, volcanic eruptions, vegetation forest fires, and meteoric dust) as well as from anthropogenic activities (e.g. mining, smelting, refining, manufacture of stainless steel and other nickel-containing alloys, fossil fuel combustion, and waste incineration). Estimates for the emission of nickel into the atmosphere from natural sources range from 8.5 million kg/year in the 1980s to 30 million kg/year in the early 1990s (ATSDR, 2005). The general population is exposed to low levels of nickel in ambient air, water, food, and through tobacco consumption.

1.4.1 Natural occurrence

Nickel is widely distributed in nature and is found in animals, plants, and soil (EVM, 2002). It is the 24th most abundant element, forming about 0.008% of the earth's crust (0.01% in igneous rocks). The concentration of nickel in soil is approximately 79 ppm, with a range of 4–80 ppm (EVM, 2002; ATSDR, 2005).

1.4.2 Air

Nickel is emitted to the atmosphere from both natural and anthropogenic sources. It has been estimated that approximately 30000 tonnes of nickel may be emitted per year to the atmosphere from natural sources. The anthropogenic emission rate is estimated to be between 1.4–1.8 times higher than the natural emission rate.

The two main natural sources are volcanoes and windblown dust from rocks and soil, estimated to respectively contribute 14000 tonnes/year and 11000 tonnes/year (NTP, 2000; Barbante *et al.*, 2002). Other relatively minor sources include: wild forest fires (2300 tonnes/year), sea salt spray (1300 tonnes/year), continental particulates (510 tonnes/year), marine (120 tonnes/year), and continental volatiles (100 tonnes/year) (Barbante *et al.*, 2002).

Anthropogenic activities release nickel to the atmosphere, mainly in the form of aerosols (ATSDR, 2005). Fossil fuel combustion is reported to be the major contributor of atmospheric nickel in Europe and the world, accounting for 62% of anthropogenic emissions in the 1980s (Barbante *et al.*, 2002; ATSDR, 2005). In 1999, an estimated 570000 tons of nickel were released from the combustion of fossil fuels worldwide (Rydh & Svärd, 2003). Of this, 326 tons were released from electric utilities (Leikauf, 2002). Of the other anthropogenic sources, nickel metal and refining accounted for 17% of total emissions, municipal incineration 12%, steel production 3%, other nickel-containing alloy production 2%, and coal combustion 2% (ATSDR, 2005).

Atmospheric nickel concentrations are higher in rural and urban air (concentration range: 5–35 ng/m^3) than in remote areas (concentration range: 1–3 ng/m^3) (WHO, 2007).

1.4.3 Water

Particulate nickel enters the aquatic environment from a variety of natural and anthropogenic sources. Natural sources include the weathering and dissolution of nickel-containing rocks and soil, disturbed soil, and atmospheric deposition. Anthropogenic sources include: industrial processes (e.g. mining and smelting operations), industrial waste water and effluent (e.g. tailings piles run-off), domestic waste water, and landfill leachate (NTP, 2000; ATSDR, 2005; WHO, 2007). Several factors influence the concentration of nickel in groundwater and surface water including: soil use, pH, and depth of sampling (WHO, 2007). Most nickel compounds are relatively water soluble at low pH (i.e. pH < 6.5). As a result, acid rain tends to increase the mobility of nickel in soil, which, in turn, has a corresponding impact on nickel concentrations in groundwater (NTP, 2000; WHO, 2007).

Based on measurement data from the 1980s, the following average nickel concentrations have been reported for groundwater, seawater and surface water, respectively: < 20 µg/L, 0.1–0.5 µg/L, and 15–20 µg/L (NTP, 2000; ATSDR, 2005). Nickel concentrations as high as 980 µg/L have been measured in groundwater with pH < 6.2 (WHO, 2007). Levels of dissolved nickel ranging from < 1–87 µg/L have been reported in urban storm run-off water samples (ATSDR, 2005).

Nickel concentrations in the range of 6–700 pg/g have been measured in high-altitude snow and ice near the summit of Mont Blanc on the French-Italian border. Seasonal variations were observed, with higher concentrations in the summer layers than in the winter layers.

Nickel levels appeared to be more associated with anthropogenic inputs (e.g. oil combustion from power generation, automobile and truck traffic) than with natural sources, such as rock and soil dust (Barbante *et al.*, 2002).

1.4.4 Soil and sediments

Natural and anthropogenic sources (e.g. mining and smelting, coal fly ash, bottom ash, metal manufacturing waste, commercial waste, atmospheric fall-out and deposition, urban refuse, and sewage sludge) contribute to the levels of nickel found in soil and sediments (NTP, 2000; ATSDR, 2005). Of the nickel emitted to the environment, the largest releases are to the soil. In 2002, estimated releases of nickel and nickel compounds from manufacturing and processing facilities (required to report to the US Toxic Release Inventory Program) were approximately 5530 and 14800 metric tonnes, respectively—accounting for 82% and 87% of estimated total nickel releases to the environment (ATSDR, 2005).

In a study of urban soil quality, a harmonized sampling regime was used to compare concentrations of nickel in six European cities differing markedly in their climate and industrial history. The sites were as far as possible from current point sources of pollution, such as industrial emissions, but all were bordered by major roads, and are thus likely to have been affected by vehicle emissions. To assess the vertical distribution of soil parameters, two depths were sampled at each point: a surface sample at 0–10 cm and a subsurface sample at 10–20 cm. The surface sample mean nickel concentration was in the range of 11–207 mg /kg, and the corresponding mean concentration in the subsurface sample, 10–210 mg/kg (Madrid *et al.*, 2006).

1.5 Human exposure

1.5.1 Exposure of the general population

Ingestion of nickel in food, and to a lesser degree in drinking-water, is the primary route of exposure for the non-smoking general population. Exposure may also occur via inhalation of ambient air and percutaneous absorption (NTP, 2000; ATSDR, 2005; WHO, 2007). The daily intake of nickel from food and beverages varies by foodstuff, by country, by age, and by gender (EVM, 2002; ATSDR, 2005). Data from a study in the USA give estimates of daily dietary intakes in the range of 101–162 µg/day for adults, 136–140 µg/day for males, and 107–109 µg/day for females. Estimates for pregnant and lactating women are higher with average daily intakes of 121 µg/day and 162 µg/day, respectively (ATSDR, 2005). Based on the concordance between different studies of dietary intake, diet is reported to contribute less than 0.2 mg/day (WHO, 2007).

Inhalation of nickel from ambient air is generally a minor route of exposure for the general population. The following daily intakes of nickel have been estimated: less than 0.05 µg/day in the USA; 0.42 µg/day (mean ambient concentration) and 15 µg/day (highest ambient concentration) in the Sudbury basin region in Ontario, Canada; and, 122 µg/day (based on the highest ambient reported nickel concentration) in the Copper Cliff region of Ontario, Canada. These estimates are based on a breathing rate of 20 m^3/day, and nickel concentrations of 2.2 ng/m^3, 21 ng/m^3, 732 ng/m^3, and 6100 ng/m^3, respectively (ATSDR, 2005).

1.5.2 Occupational exposure

Nickel, in the form of various alloys and compounds, has been in widespread commercial use for over 100 years. Several million workers worldwide are exposed to airborne fumes, dusts and mists containing nickel and its compounds. Exposures by inhalation, ingestion or skin

contact occur in nickel-producing industries (e.g. mining, milling, smelting, and refining), as well as in nickel-using industries and operations (e.g. alloy and stainless steel manufacture; electroplating and electrowinning; welding, grinding and cutting). Insoluble nickel is the predominant exposure in nickel-producing industries, whereas soluble nickel is the predominant exposure in the nickel-using industries. Occupational exposure results in elevated levels of nickel in blood, urine and body tissues, with inhalation as the main route of uptake (IARC, 1990; NTP, 2000).

Estimates of the number of workers potentially exposed to nickel and nickel compounds have been developed by the National Institute of Occupational Safety and Health (NIOSH) in the USA and by CAREX (CARcinogen EXposure) in Europe. Based on the National Occupation Exposure Survey (NOES), conducted during 1981–1983, NIOSH estimated that 507681 workers, including 19673 female workers, were potentially exposed to 'Ni, Nickel-MF Unknown' (agent code: 50420) in the workplace (NIOSH, 1990). The following six industries accounted for nearly 60% of exposed workers: 'fabricated metal products' (n = 69984), 'special trade contractors' (n = 55178), 'machinery, except electrical' (n = 55064), 'transportation equipment' (n = 44838), 'primary metal industries' (n = 39467), and 'auto repair, services, and garages' (n = 27686). Based on occupational exposure to known and suspected carcinogens collected during 1990–1993, the CAREX database estimates that 547396 workers were exposed to nickel and nickel compounds in the European Union. Over 83% of these workers were employed in the 'manufacture of fabricated metal products, except machinery and equipment' (n = 195597), 'manufacture of machinery, except electrical' (n = 122985), 'manufacture of transport equipment' (n = 64720), 'non-ferrous base metal industries' (n = 32168), 'iron and steel basic industries' (n = 26504), and 'metal ore mining' (n = 16459). CAREX Canada (2011) estimates that approximately 50000 Canadians are exposed to nickel in the workplace (95% male). Exposed industries include: commercial/industrial machinery and equipment repair/maintenance; architectural, structural metals manufacturing; specialty trade contractors; boiler, tank and shipping container manufacturing; metal ore mining; motor vehicle parts manufacturing; machine shops, turned product, screw, nut and bolt manufacturing; coating, engraving, heat treating and allied activities; iron/steel mills and ferro-alloy manufacturing; non-ferrous metal production and processing.

Historically, metallic nickel exposures tended to be higher in nickel-producing industries than in the nickel-using industries, with estimates of historical mean levels of exposure to inhalable metallic nickel in the range of 0.01–6.0 mg/m^3 and 0.05–0.3 mg /m^3, respectively. However, data from the EU suggest that occasional higher exposures to inhalable metallic nickel may be present in certain industry sectors (Sivulka, 2005).

Data on early occupational exposures to nickel and nickel compounds were summarized in the previous *IARC Monograph* (IARC, 1990). Data from studies and reviews on nickel exposure published since the previous *IARC Monograph* are summarized below for both the nickel-producing and the nickel-using industries.

(a) Studies of nickel-producing industries

Ulrich *et al.* (1991) collected data on several indicators of nickel exposure (stationary and personal air sampling; urinary nickel excretion) among electrolytic nickel production workers in the Czech Republic (formerly, Czechoslovakia). Air samples (n = 52) were collected on membrane filters and analysed by electrothermal atomic absorption spectrometry. Urine samples (n = 140) were collected during the last 4 hours of workers' shifts, and the results were corrected to a standard density of 1.024. In a matched-pair analysis of air and urine samples collected from 18 electrolysis workers, the correlation coefficient

was 0.562; the mean concentration of nickel in urine was 53.3 µg/L (range, 1.73–98.55 µg/L), and the mean concentration in air was 0.187 mg/m^3 (range, 0.002–0.481 mg/m^3).

In a study conducted at a Finnish electrolytic nickel refinery, Kiilunen *et al.* (1997) collected data on nickel concentrations in air, blood, and urine. Stationary samples (n = 141) were collected from 50 locations in the refinery, including those areas where breathing zone samples were taken. Personal (i.e. 8-hour breathing zone) samples were collected over 4 successive work days (n = 157), from the shoulders when no respiratory protection was worn, inside the mask when protective equipment was worn, and inside the mask hanging on the shoulder of the worker when the mask was taken off. Historical occupational hygiene measurements were examined to assess past exposure. Spot urine samples (n = 154) were collected, pre- and post-shift, over 4 successive work days and 1 free day thereafter. Blood samples (n = 64) were collected at the beginning of the study and at the end of the last work shift. A total of 34 workers (of 100) volunteered to participate in the study. Urinary nickel results in the workers were compared with two non-exposed control groups (30 office workers from the refinery and 32 unexposed persons from the Helsinki area). For the stationary samples, nickel concentrations were reported by location as water-soluble nickel, acid-soluble nickel and total nickel (all in µg/m^3). Geometric mean nickel concentrations ranged from: 7.4 µg/m^3 ('other sites') to 451 µg/m^3 (in 'tank house 3′) for water-soluble nickel; 0.5 µg/m^3 ('other sites') to 4.6 µg/m^3 ('solution purification') for acid-soluble nickel; and, 7.6 µg/m^3 ('other sites') to 452 µg/m^3 (in 'tank house 3′). For the breathing zone samples, the range of geometric mean nickel concentrations was 0.2–3.2 µg/m^3 (inside the mask) and 0.6–63.2 µg/m^3 (no mask). Based on a review of historical stationary sampling data, average nickel concentrations varied in the range of 230–800 µg/m^3 over the period 1966–88. Lower concentrations (112–484 µg/m^3) were observed in the early 1990s. Geometric mean after-shift urinary concentrations of nickel were in the range of 0.1–0.8 µmol/L (mask in use) and 0.5–1.7 µmol/L (no mask in use). Urinary nickel concentrations were still elevated after 2- and 4-week vacations. No consistent correlations between airborne nickel concentrations and nickel concentrations in the blood or urine were observed.

Thomassen *et al.* (2004) measured the exposure of 135 copper refinery workers (45 females, 90 males) to copper, nickel and other trace elements at a nickel refinery complex in Monchegorsk, the Russian Federation. Full-shift breathing zone samples were collected for workers in the pyrometallurgical process (n = 138) and in the electrorefining process (n = 123) areas. Workers wore personal samplers for two to four full shifts. IOM samplers were used to assess the inhalable aerosol fraction, and Respicon samplers (3-stage virtual impactors) were used to separate the inhalable fraction into respirable, tracheobronchal, and extrathoracic aerosol fractions. The geometric mean inhalable nickel concentration was in the range of 0.024–0.14 mg/m^3 for samples taken in the pyrometallurgical areas, and 0.018–0.060 mg/m^3 for samples taken in the electrorefining areas (data presented as the sum of the inhalable water-soluble and water-insoluble subfractions). For the inhalable aerosol nickel concentrations observed in the pyrometallurgical process steps, the water-insoluble subfraction contained higher levels than the water-soluble fraction, with geometric means of 59 µg/m^3 and 14 µg/m^3, respectively. In the electrorefining process area, the nickel concentrations in the inhalable subfractions were 14 µg/m^3 (water-soluble) and 10 µg/m^3 (water-insoluble).

Air monitoring was conducted in three areas of a nickel base metal refinery in South Africa (the ball mill area, the copper winning area, and the nickel handling area). Personal breathing zone samples (n = 30) were collected in all areas of the

plant, and were analysed gravimetrically and by inductively coupled plasma mass spectroscopy. The mean time-weighted average concentrations for soluble, insoluble and total nickel dust, respectively, were 44, 51, and 95 μg/m³ in the ball mill area; 395, 400, and 795 μg/m³ in the nickel handling area; and 46, 17, and 63 μg/m³ in the copper winning area (Harmse & Engelbrecht, 2007).

Airborne dust concentrations, nickel concentrations, nickel speciation, and aerosol particle size distributions in two large-scale nickel production facilities were assessed by collecting a total of 46 inhalable samples (30 personal, 16 area), and 28 cascade impactor samples (18 personal, 10 area). Samples were collected using IOM and Marple cascade impactor sampling heads, and analysed gravimetrically. At the first site, inhalable concentrations were in the range of 0.5–9.1 mg/m³ for the personal samples, and 0.2–5.7 mg/m³ for the area samples (median concentrations, 0.7 mg/m³ and 0.4 mg/m³, respectively). Total nickel levels in the personal samples were in the range of 1.8–814.9 μg/m³, and 19.8–2481.6 μg/m³ in the area samples (median concentrations, 24.6 μg/m³ and 92.0 μg/m³, respectively). At the second site, airborne concentrations of inhalable dust were in the range of 1.2–25.2 mg/m³ for the personal samples, and 1.5–14.3 mg/m³ (median concentrations, 3.8 mg/m³ and 2.9 mg/m³, respectively) for the area samples. Total nickel levels were in the range of 36.6–203.4 μg/m³ in the area samples, and 0.2–170.7 μg/m³ in the personal samples (median concentrations, 91.3 and 15.2 μg/m³, respectively) (Creely & Aitken, 2008).

(b) Studies of nickel-using industries

Bavazzano *et al.* (1994) collected air, face, hand, and spot urine samples from 41 male workers in electroplating operations in 25 small factories in the province of Florence, Italy, and compared them to samples collected from non-exposed male subjects (face and hand samples: n = 15 subjects aged 15–60 years old; urine samples: n = 60 subjects aged 22–63 years old). For the airborne nickel measurements, personal exposure were in the range of 0.10–42 μg/m³ (median concentration, 2.3 μg/m³). The median nickel levels in the urine, on the hands, and on the face were, respectively, 4.2 μg/L (range, 0.7–50 μg/L), 39 μg (range, 1.9–547 μg), and 9.0 μg (range, 1.0–86 μg). Median hand, face, and urine nickel levels for the control subjects were, respectively, 0.8 μg (range, 0.0–5.3 μg; n = 15), 0.30 μg (range, 0.0–2.4; n = 15), and 0.7 μg (range, 0.1–2.5 μg; n = 60).

In an occupational hygiene survey of 38 nickel electroplating shops in Finland, exposure to nickel was assessed by questionnaire (n = 163), urine samples (phase 1: n = 145; phase 2: n = 104), bulk samples (n = 30), and air measurements in three representative shops (one clean, one intermediate, one dirty) on 1 day during which urine samples were also being collected. Full-shift breathing zone samples were collected from inside and outside a respirator with filters. In the first phase of the study, average urinary nickel concentration was 0.16 μmol/L (range, 0.0–5.0 μmol/L; n = 145). The range of mean values for different workplaces was 0.01–0.89 μmol/L, and for the median values, 0.02–0.05 μmol/L. For the 97 workers followed in the second phase, urinary nickel concentrations were observed to fluctuate with exposure, with mean nickel concentrations in the range of 0.10–0.11 μmol/L for the morning specimens, and 0.12–0.16 μmol/L for the afternoon specimens. Personal breathing zone nickel concentrations were as follows: 0.5 μg/m³ (hanger worker in the 'clean shop'), 0.7 μg/m³ (worker responsible for maintenance of nickel bath in the 'clean' shop), and in the range of 5.6–78.3 μg/m³ for workers (n = 6) in the 'dirty' shop. In the area samples, nickel concentrations were 26 μg/m³ (near the nickel bath in the 'clean' shop), 11.9–17.8 μg/m³ (in the hanging area of the 'dirty' shop), and 73.3 μg/m³ (beside the nickel bath in the 'dirty' shop) (Kiilunen *et al.*, 1997).

Kiilunen (1997) analysed data from the biomonitoring registry and the occupational hygiene service registry of the Finnish Institute of Occupational Health to examine trends in nickel exposure during 1980–89. A total of 1795 urinary nickel samples (for which it was possible to identify job titles) were examined, along with 260 nickel measurements from the breathing zone of workers for whom job titles were available. Across all job titles, the ranges of mean urinary nickel concentrations, by time period, were as follows: 0.05–0.52 µmol/L for 1980–82, 0.14–0.51 µmol/L for 1983–85, and 0.17–0.87 µmol/L for 1986–89. The two largest occupational groups sampled were platers (n = 503), and welders (n = 463). Mean urinary concentrations for platers, by time period, were 0.35 µmol/L for 1980–82 (range, 0.01–2.95), 0.30 µmol/L for 1983–85 (range, 0.01–2.10), and 0.38 µmol/L for 1986–89 (range, 0.03–2.37). Mean urinary concentrations for welders, by time period, were 0.22 µmol/L for 1980–82 (range, 0.03–1.58), 0.17 µmol/L for 1983–85 (range, 0.03–0.65), and 0.21 µmol/L for 1986–89 (range, 0.01–1.58). Analysis of the breathing zone measurements revealed that 22.1% of all measurements in 1980–82 had exceeded the occupational exposure limit (OEL) of 0.1 mg/m^3. Similar results were seen for the 1983–85 period (24.8%), rising to 30.7% for the 1986–89 period. Job titles with mean values over the OEL in 1983–85 included: grinders (mean, 0.76 mg/m^3, n = 29), one metal worker (0.12 mg/m^3), powder cutters (mean, 0.34 mg/m^3, n = 31), one spray painter (0.20 mg/m^3), and welders (0.17 mg/m^3, n = 72). Mean levels exceeded the OEL in the following four occupational groups during 1986–89: carbon arc chisellers (mean, 0.6 mg/m^3, n = 2), grinders (mean, 0.28 mg/m^3, n = 19), one warm handler (0.18 mg/m^3), and burn cutters (mean, 0.14 mg/m^3, n = 2).

The association between occupational exposure to airborne nickel and nickel absorption was examined by collecting personal breathing zone samples and urine samples from 10 workers at a galvanizing plant in Brazil that uses nickel sulfate. Spot urine samples were collected pre- and post-shift from the nickel-exposed workers over 5 consecutive days, and from 10 non-nickel exposed workers employed at a zinc plant over 3 consecutive days (n = 97 and 55, respectively). Both groups completed a questionnaire on occupational history, health and lifestyle factors; exposed workers also underwent a medical examination. Personal breathing zone samples (first 4 hours of shift) were collected using NIOSH protocols. Geometric mean airborne nickel levels were in the range of 2.8–116.7 µg/m^3, and the urine levels, from samples taken post-shift, were in the range of 4.5–43.2 µg/g creatinine (mean, 14.7 µg/g creatinine) (Oliveira *et al.*, 2000).

Sorahan (2004) examined data on mean (unadjusted) levels of exposure to inhalable nickel at a nickel alloy plant during 1975–2001 in Hereford, the United Kingdom. Data were reported for two time periods: 1975–80 and 1997–2001. Mean nickel levels (unadjusted) for the earlier period were as follows: 0.84 mg/m^3 in the melting, fettling, and pickling areas; 0.53 mg/m^3 in the extrusion and forge, hot strip and rolling, engineering, and melting stores areas; 0.55 mg/m^3 in the machining, hot rolling, Nimonic finishing, and craft apprentice areas; 0.40 mg/m^3 in the roll turning and grinding, cold rolling, cold drawing, wire drawing, and inspection areas; and 0.04 mg/m^3 in the process stock handling, distribution and warehouse areas. The corresponding mean nickel levels (unadjusted) for the latter period were: 0.37 mg/m^3, 0.45 mg/m^3, 0.31 mg/m^3, 0.30 mg/m^3, and 0.29 mg/m^3, respectively.

Eight-hour TWA (8-h TWA) exposures calculated for the period 1997–2001 were 0.33 mg/m^3, 0.31 mg/m^3, 0.16 mg/m^3, 0.16 mg/m^3, and 0.27 mg/m^3, respectively.

Sorahan & Williams (2005) assessed the mortality of workers at a nickel carbonyl refinery in Clydach, the United Kingdom to determine whether occupational exposure to nickel resulted in increased risks of nasal cancer and lung cancer.

Using personal sampling data collected in the 1980s and 1990s, 8-h TWA exposure to total inhalable nickel was calculated, and assigned to six categories of work, based on the predominant species of nickel exposure. The six categories of work were: feed handling and nickel extraction, including kilns (oxide/metallic); pellet and powder production, and shipping (metallic); nickel salts and derivatives, and effluent (metallic/soluble); wet treatment and related processes (metallic/subsulfide/soluble); gas plant (non-nickel); and engineering and site-wide activities that could include any of the preceding work areas. Mean levels of total inhalable nickel dust were in the range of 0.04–0.57 mg/m^3 in the 1980s (n = 1781), and 0.04–0.37 mg/m^3 in the 1990s (n = 1709).

Stridsklev *et al.* (2007) examined the relationship between the concentration of airborne nickel in the occupational environment of grinders (n = 9) grinding stainless steel in Norway and the concentration of nickel in their urine and blood. Grinders either worked in a well ventilated hall of a shipyard or in a small non-ventilated workshop. The sampling protocol was as follows: full-shift personal samples were collected in the breathing zone of grinders over the course of 1 work week; urine samples were collected three times daily for 1 week (first void in the morning, pre- and post-shift); and blood samples were drawn twice daily for 3 days in 1 week (pre- and post-shift). Blood and urine samples were also collected on the Monday morning after a 3-week vacation in the workshop. Grinders also completed a questionnaire to collect information on work history, use of personal protective equipment, and smoking habits. Mean levels of airborne nickel were 18.9 µg/m^3 (range, 1.8–88.6 µg/m^3) in the shipyard, and 249.8 µg/m^3 (range, 79.5–653.6 µg/m^3) in the workshop. Mean blood nickel levels for grinders were 0.87 µg/L (range, < 0.8–2.4 µg/L) in whole blood, and 1.0 µg/L (range, < 0.4–4.1 µg/L) in plasma. Mean urinary nickel levels for grinders were 3.79 µg/g creatinine (range, 0.68–10.6 µg/g creatinine), 3.39 µg/g creatinine (range, 0.25–11.1 µg/g creatinine), and 4.56 µg/g creatinine (range, < 0.53–11.5 µg/g creatinine), from the first void, pre- and post-shift samples, respectively. With the exception of stainless steel welders welding the MIG/MAG-method [Metal Inert Gas-Metal Active Gas], mean urinary nickel levels were higher in grinders than in welders. Mean urinary nickel levels in MIG/MAG welders were 5.9 µg/g creatinine (range, < 0.24–20.5 µg/g creatinine), 3.8 µg/g creatinine (range, 0.33–11.4 µg/g creatinine), and 4.6 µg/g creatinine (range, < 0.25–18.4 µg/g creatinine) from the first void, pre-, and post-shift samples, respectively.

Sivulka & Seilkop (2009) reconstructed historical exposures to nickel oxide and metallic nickel in the US nickel alloy industry from personal and area measurements collected at 45 plants since the 1940s (n = 6986 measurements). Of the measurements included in the database, 96% were personal breathing zone samples, and 4% were stationary area samples. The data provided evidence of a strongly decreasing gradient of airborne total nickel levels from the 1940s to the present.

1.5.3 Dietary exposure

Nickel has been measured in a variety of foodstuffs as "total nickel." Average concentrations are in the range of 0.01–0.1 mg/kg, but can be as high as 8–12 mg/kg in certain foods (EVM, 2002; WHO, 2007). Factors influencing the concentration of nickel in food include the type of food (e.g. grains, vegetables, fruits versus seafood, mother's milk versus cow's milk), growing conditions (i.e. higher concentrations have been observed in food grown in areas of high environmental or soil contamination), and food preparation techniques (e.g. nickel content of cooking utensils, although the evidence for leaching from stainless steel cookware is somewhat mixed) (EVM, 2002; WHO, 2007).

The highest mean concentrations of nickel have been measured in beans, seeds, nuts and grains (e.g. cocoa beans, 9.8 µg/g; soyabeans, 5.2 µg/g; soya products, 5.1 µg/g; walnuts, 3.6 µg/g; peanuts, 2.8 µg/g; oats, 2.3 µg/g; buckwheat, 2.0 µg/g; and oatmeal, 1.8 µg/g). Although nickel concentrations vary by type of foodstuff, average levels are generally within the range of 0.01–0.1 µg/g. Reported ranges for some common food categories are: grains, vegetables and fruits, 0.02–2.7 µg/g; meats, 0.06–0.4 µg/g; seafood, 0.02–20 µg/g; and dairy, < 100 µg/L (EVM, 2002). This variability in nickel content makes it difficult to estimate the average daily dietary intake of nickel (EVM, 2002).

1.5.4 Biomarkers of exposure

Biomarker levels are influenced by the chemical and physical properties of the nickel compound studied, and by the time of sampling. It should be noted that the nickel compounds, the timing of collection of biological samples (normally at the end of a shift), and the analytical methods used differ from study to study, and elevated levels of nickel in biological fluids and tissue samples are mentioned only as indications of uptake of nickel, and may not correlate directly to exposure levels (IARC, 1990).

Atomic absorption spectrometry (AAS) and inductively coupled plasma atomic emission spectroscopy (ICP-AES) are the most common analytical methods used to determine "total nickel" concentrations in biological materials (such as blood, tissues, urine, and faeces). Nickel content can also be measured in other tissues, such as nails and hair, although specific procedures for dissolving the sample must be followed (ATSDR, 2005). The presence of calcium, sodium or potassium interferes with the quantification of nickel in biological samples, and specific techniques (e.g. isotope dilution) must be used to validate nickel measurements (ATSDR, 2005). Serum and urine samples are the most useful biomarkers of recent exposure, reflecting the amount of nickel absorbed in the previous 24–48 hours (NTP, 2000).

Minoia *et al.* (1990) used atomic absorption spectroscopy and neutron activation analysis to determine trace element concentrations of nickel in urine, blood, and serum collected from non-exposed healthy subjects (n = 1237; 635 males, 602 females) from the Lombardy region of northern Italy. The mean nickel level in urine samples (n = 878) was 0.9 µg/L (range, 0.1–3.9 µg/L); in blood samples (n = 36), 2.3 µg/L (range, 0.6–3.8 µg/L); and in serum samples (n = 385), 1.2 µg/L (range, 0.24–3.7 µg/L).

In a Norwegian-Russian population-based health study, human nickel exposure was investigated in the adult population living near a nickel refinery on both sides of the Norwegian-Russian border during 1994–95. Urine samples were collected from inhabitants, aged 18–69 years, of Nikel, Zapolyarny, and Sor-Varanger and also from individuals living more remotely from the Kola Peninsula nickel-producing centres (in the Russian cities of Apatity and Umba, and the Norwegian city of Tromso). A total of 2233 urine specimens were collected and analysed for nickel using electrothermal atomic absorption spectrometry. The highest urinary nickel concentrations were observed in residents of Nikel (median, 3.4 µg/L; mean, 4.9 µg/L; range, 0.3–61.9 µg/L), followed by Umba (median, 2.7 µg/L; mean, 4.0 µg/L; range, 1.0–17.0 µg/L), Zapolyarny (median, 2.0 µg/L; mean, 2.8 µg/L; range, 0.3–24.2 µg/L), Apatity (median, 1.9 µg/L; mean, 2.6 µg/L; range, 0.3–17.0 µg/L), Tromso (median, 1.2 µg/L; mean, 1.4 µg/L; range, 0.3–6.0 µg/L), and Sor-Varanger (median, 0.6 µg/L; mean, 0.9 µg/L; range, 0.3–11.0 g/L). The Russian participants all had a higher urinary nickel average than those from Norway, regardless of geographic location (Smith-Sivertsen *et al.*, 1998).

Ohashi *et al.* (2006) determined reference values for nickel in urine among women of the general population of 11 prefectures in Japan.

A total of approximately 13000 urine samples were collected in 2000–05 from 1000 adult women aged 20–81 years who had no occupational exposure to nickel. Nickel in urine was analysed by graphite furnace atomic absorption spectrometry. The observed geometric mean concentration for nickel was 2.1 μg/L (range, < 0.2–57 μg/L). After correction for creatinine, the geometric mean concentration was reported as 1.8 μg/L (maximum, 144 μg/L).

1.5.5 Other sources of exposure

Nickel, chromium, and cobalt are common causes of allergic contact dermatitis. In the early 1990s it was recommended that household and other consumer products should not contain more than 5 ppm of each of nickel, chromium, or cobalt, and that, for an even greater degree of protection, the ultimate target level should be 1 ppm. In a recent survey, selected consumer products had the following nickel levels (ppm): hand-wash powders, 0.9; heavy duty powders, 0.5; laundry tablets, 0.5; liquid/powder cleaners, 0.4; heavy duty liquids, 0.1; machine/hand-wash liquids, 0.1; hand-wash liquids, 0.1, fine wash liquids, 0.1; and dishwashing liquids, 0.1 (Basketter *et al.*, 2003).

Potential iatrogenic sources of exposure to nickel are dialysis treatment, leaching of nickel from nickel-containing alloys used as prostheses and implants, and contaminated intravenous medications (Sunderman, 1984).

2. Cancer in Humans

The previous *IARC Monograph* was based upon evidence of elevated risk of lung and nasal cancers observed among workers involved in a variety of nickel sulfide ore smelting and nickel refining processes that included high-temperature processing of nickel matte, nickel–copper matte, electrolytic refining, and Mond process refining. The exposures included metallic nickel, nickel oxides, nickel subsulfide, soluble nickel compounds, and nickel carbonyl. These cohort studies were conducted mainly in Canada, Norway, Finland, and in the United Kingdom (IARC, 1990; ICNCM, 1990).

2.1 Cohort studies and nested case–control studies

Since the previous *IARC Monograph*, several studies have extended follow-up to some of the previous cohorts, and have provided additional cohort and nested case–control analyses related mostly to lung cancer risk, and taking into account potential confounding factors as well as mixed exposures to water-soluble and -insoluble nickel compounds. Among the most common occupations with exposure to nickel compounds are stainless steel welders, who are also exposed to chromium (VI) compounds, and other compounds. Although there have been some cohort studies of stainless steel welders, these are not recorded in the present *Monograph* because it is difficult to ascribe any excess risks in these cohorts to nickel compounds specifically. Key results of some of these cohort studies can be found in Table 2.1 of the *Monograph* on chromium (VI) in this volume.

Also, since the previous *IARC Monograph*, experimental evidence has become available that nickel metal dust can become solubilized and bioavailable after inhalation. Consequently, separately classifying nickel and nickel compounds was viewed by the Working Group as not warranted. A similar distinction has not been made for other metals, e.g. beryllium and cadmium, in other *IARC Monographs*. Accordingly, this review did not exclude studies that focused on metallic nickel, unless they, for other reasons, were considered uninformative.

2.1.1 Cancer of the lung

Studies were carried out in nickel smelters and refineries in Canada, Norway (Kristiansand), Finland, and the United Kingdom (Clydach). Because the refining processes differed in the plants, the exposure profiles to various nickel compounds were different across the cohorts. Nonetheless, increased risks for lung cancer were found in cohorts from all of these facilities (see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.1.pdf).

High risks for lung cancers were observed among calcining workers in Canada, who were heavily exposed to both sulfidic and oxidic nickel (nickel sulfides and oxides). A high lung cancer rate was also seen among nickel plant cleaners in Clydach who were heavily exposed to these insoluble compounds, with little or no exposure to soluble nickel. The separate effects of oxides and sulfides could not be estimated, however, as high exposure was always either to both, or to oxides together with soluble nickel. Workers in Clydach calcining furnaces and nickel plant cleaners, exposed to high levels of metallic nickel, had high lung cancer risks (see Table 2.1 online). A substantial excess risk for lung cancer among hydrometallurgy workers in Norway was mainly attributed to their exposure to water-soluble nickel. Their estimated exposures to other types of nickel (metallic, sulfidic, and oxidic) were as much as an order of magnitude lower than those in several other areas of the refinery, including some where cancer risks were similar to those observed in hydrometallurgy. High risks for lung cancer were also observed among electrolysis workers at Kristiansand (Norway). These workers were exposed to high estimated levels of soluble nickel and to lower levels of other forms of nickel. Nickel sulfate and nickel chloride (after 1953) were the only or predominant soluble nickel species present in these areas.

An update of the Kristiansand cohort by Andersen *et al.* (1996) demonstrated a dose–response relationship between cumulative exposure to water-soluble nickel compounds and lung cancer ($P < 0.001$) when adjustment was made for age, smoking, and nickel oxide. The risk was increased 3-fold in the highest soluble nickel dose group. A lesser, but positive, effect was seen between cumulative exposure to nickel oxide and risk of lung cancer, also with adjustment for age, cigarette smoking, and exposure to water-soluble nickel (P for trend = 0.05, see Table 2.2).

Subsequent to the Andersen *et al.* (1996) study, an industrial hygiene study re-evaluated exposure among the Norwegian refinery workers based on new information related to nickel species and exposure levels (Grimsrud *et al.*, 2000). Grimsrud *et al.* (2003) updated the lung cancer incidence among the Norwegian nickel refinery workers (see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.3.pdf). The strongest gradient for cumulative exposure and lung cancer was found in relation to water-soluble nickel adjusted for cigarette-smoking habits, which was known for 4728 (89%) of the cohort members. Regarding species of water-soluble nickel compounds, the risk from potential exposure to nickel chloride was similar to that for nickel sulfate. The nickel electrolysis process (using nickel sulfate) changed to a nickel-chloride-based process in 1953, and workers hired in 1953 or later had a similar lung cancer risk (standardized incidence ratio [SIR], 4.4; 95%CI: 1.8–9.1) as for those employed in the same area before 1953 when the nickel sulfate was used (SIR, 5.5; 95%CI: 3.0–9.2). Analyses by year of first employment indicated that those initially employed after 1978 continued to demonstrate a significantly elevated risk of lung cancer (SIR, 3.7; 95%CI: 1.2–8.7), suggesting continued exposure to nickel compounds.

Grimsrud *et al.* (2002) conducted a case–control study of lung cancer nested within the

Table 2.2 Relative risks of lung cancer by cumulative exposure to soluble nickel and nickel oxide, considering the two variables simultaneously by multivariate Poisson regression analysis[a]

Variable	Mean exposure (mg/m^3)	Cases	Relative risk	95%CI	Test for linear trend
Soluble nickel					$P < 0.001$
< 1	0.1	86	1.0	Referent	
1–4	2.3	36	1.2	0.8–1.9	
5–14	8.8	23	1.6	1.0–2.8	
≥ 15	28.9	55	3.1	2.1–4.8	
Nickel oxide					$P = 0.05$
< 1	0.4	53	1.0	Referent	
1–4	2.5	49	1.0	0.6–1.5	
5–14	8.3	53	1.6	1.0–2.5	
≥ 15	44.3	45	1.5	1.0–2.2	

[a] Workers with unknown smoking habits were excluded (three cases of lung cancer).
Adjusted for smoking habits and age.
From Andersen *et al.* (1996)

cohort of Norwegian nickel refinery workers (see Table 2.3 online). Exposure groups were determined based on quintiles of the exposure variables in the controls. Analyses by cumulative exposure adjusted for cigarette smoking indicated that odds ratios for lung cancer in the highest cumulative exposure category of water-soluble nickel, sulfidic nickel, metallic nickel, and oxidic nickel were 3.8 (95%CI: 1.6–9.0), 2.8 (95%CI: 1.1–6.7), 2.4 (95%CI: 1.1–5.3), and 2.2 (95%CI: 0.9–5.4), respectively. The trend for cumulative exposure and lung cancer was significant for water-soluble nickel compounds only ($P = 0.002$). There was, however, a high degree of correlation with exposure to nickel and nickel compounds as a whole, making evaluation of the independent effect of individual compounds difficult. Nonetheless, when data were further adjusted for exposure to water-soluble compounds, there were no significant trends in the odds ratios by cumulative exposure to sulfidic, oxidic, or metallic nickel. The odds ratios related to the highest cumulative exposure group for each of these compounds were 1.2 (95%CI: 0.5–3.3), 0.9 (95%CI: 0.4–2.5), and 0.9 (95%CI: 0.3–2.4), respectively (see Table 2.4). In further analyses, with adjustment for cigarette smoking, arsenic, asbestos, sulfuric acid mist, cobalt and occupational carcinogenic exposures outside the refinery, the strong association between lung cancer and water-soluble nickel remained (Grimsrud *et al.*, 2005).

Anttila *et al.* (1998) updated an earlier cohort study of Finnish nickel refinery and copper/nickel smelter workers (Karjalainen *et al.*, 1992). Among refinery workers employed after 1945, who were exposed primarily to nickel sulfate, an excess of lung cancer was observed in the overall cohort (SIR, 2.61; 95%CI: 0.96–5.67), and the lung cancer risk increased with > 20 years of latency (SIR, 3.38; 95%CI: 1.24–7.36, based on six cases). Among smelter workers, lung cancer was also elevated in the overall cohort (SIR, 1.39; 95%CI: 0.78–2.28), and, similarly, a significant increase in lung cancer risk with > 20 years of latency was observed (SIR, 2.00; 95%CI: 1.07–3.42).

There have been three subsequent reports that provide additional information on refinery workers in Wales (the United Kingdom) exposed to nickel carbonyl and other nickel compounds.

Easton *et al.* (1992) carried out an updated analysis of Welsh nickel refinery workers to determine which nickel compounds were responsible for lung cancer among the 2524 workers employed

Table 2.4 Adjusted[a] odds ratios for lung cancer by exposure to sulfidic, oxidic or metallic nickel in a nested case–control study of Norwegian nickel refinery workers observed during 1952–95

Cumulative exposure to nickel[b]	Odds ratio	95% CI
Sulfidic nickel		
Unexposed	1.0	
Low	1.5	0.6–3.9
Low-medium	2.2	0.9–5.5
Medium	1.8	0.7–4.5
Medium-high	1.3	0.5–3.3
High	1.2	0.5–3.3
Likehood ratio test: $P = 0.344$		
Oxidic nickel		
Unexposed	1.0	
Low	1.5	0.6–3.8
Low-medium	1.8	0.7–4.5
Medium	1.4	0.6–3.7
Medium-high	1.5	0.6–3.7
High	0.9	0.4–2.5
Likehood ratio test: $P = 0.406$		
Metallic nickel		
Unexposed	1.0	
Low	1.2	0.5–2.9
Low-medium	1.0	0.5–2.4
Medium	1.0	0.4–2.3
Medium-high	1.0	0.4–2.4
High	0.9	0.3–2.4
Likehood ratio test: $P = 0.972$		

[a] Data were adjusted for smoking habits in five categories (never smoker, former smoker, or current smoker of 1–10, 11–20, or > 20 g/day), and for exposure to water-soluble nickel as a continuous variable with natural log-transformed cumulative exposure values (ln[(cumulative exposure) + 1]).

[b] Categories were generated according to quartiles among exposed control. In each of the three analyses, data were unadjusted for the other two insoluble forms of nickel.

From Grimsrud *et al.* (2002)

for > 5 years before the end of 1969, and followed during 1931–85. The model was based on exposures occurring before 1935, and was adjusted for age at first exposure, duration of exposure, and time since first exposure. For lung cancer, the best fitting model suggested risks for soluble and metallic nickel exposures, and much less (if any) risk for nickel oxide or sulfides. Sorahan & Williams (2005) followed during 1958–2000 a group of 812 workers from the cohort of Welsh nickel refinery workers who were hired between 1953–92, and who had achieved > 5 years of employment. The overall lung cancer SMR was 1.39 (95%CI: 0.92–2.01). For those with > 20 years since the start of employment, lung cancer risk was significantly elevated [SMR, 1.65; 95%CI: 1.07–2.41], indicating an elevated risk of lung cancer among those hired since 1953.

Grimsrud & Peto (2006) combined data from the most recent updates of Welsh nickel refinery workers to assess lung cancer mortality risk by period of initial employment. For those first employed since 1930, an elevated risk was observed for lung cancer (SMR, 1.33; 95%CI: 1.03–1.72). [The Working Group noted that

exposures were dramatically reduced during the 1920s.]

Egedahl *et al.* (2001) updated the mortality data among employees at a hydrometallurgical nickel refinery and fertilizer complex in Fort Saskatchewan, Canada, who had worked for 12 continuous months during 1954–78. Among the 718 men exposed to nickel, the lung cancer SMR was 0.67 (95%CI: 0.24–1.46, based on six deaths). Significant decreases were observed for the 'all causes of death' category (SMR, 0.57; 95%CI: 0.43–0.74), and for the 'all cancer deaths' category (SMR, 0.47; 95%CI: 0.25–0.81). [The Working Group considered the study uninformative for the evaluation of cancer risks due to a substantial healthy worker effect which may have masked excess mortality that was associated with nickel exposure.]

Goldberg *et al.* (1994) conducted a 10-year incidence study and a nested case–control study of a cohort of nickel mining (silicate-oxide ores) and refinery workers in New Caledonia, South Pacific. They observed a significant decrease in the incidence of lung cancer, and this was also observed for other respiratory cancers The results of the case–control study did not show elevated risks for respiratory cancers in relation to low levels of exposure to soluble nickel, nickel sulfide, or metallic nickel. For all three nickel exposures separately, the odds ratios were 0.7.

[The Working Group noted that in most of these studies of lung cancer risk in smelters and refineries, there was exposure to metallic nickel together with exposure to the other forms of nickel (Sivulka, 2005). Only one of these studies involved an attempt to evaluate separately the effect of metallic nickel (Grimsrud *et al.*, 2002).]

Several additional studies of workers with potential exposure to metallic nickel were reviewed by the Working Group. Arena *et al.* (1998) evaluated mortality among workers exposed to "high nickel alloys" in the USA. A recent industrial hygiene analysis indicated that oxidic nickel comprised 85% of the total nickel exposure of these workers, with the rest being mostly metallic nickel (Sivulka & Seilkop, 2009). Compared to US national rates, lung cancer was significantly elevated among white men (SMR, 1.13; 95%CI: 1.05–1.21), among non-white men the SMR was 1.08 (95%CI: 0.85–1.34), and in women 1.33 (95%CI: 0.98–1.78). [The Working Group noted that the lung cancer SMR for the entire cohort combined was 1.13 (95%CI: 1.06–1.21) based on 955 observed deaths.] The authors also calculated SMRs based on local (SMSA) rates for the separate population subgroups. When calculated for the total cohort, the resulting SMR was [1.01; 95%CI: 0.95–1.08]. [The Working Group noted that it is difficult to interpret the use of local rates when the study population was derived from 13 separate areas located throughout the USA, but the use of rates from urban areas could have overestimated the expected number of deaths from lung cancer. The Working Group noted that the overall SMR for lung cancer in this study compared with the national population was statistically significant, and provides some evidence of an association between exposures in these plants and lung cancer. It appears that the primary exposure was to nickel oxide and thus, the study cannot be used to evaluate the specific carcinogenicity of metallic nickel. Analysis of lung cancer by duration of employment did not indicate a dose–response. The Working Group noted that duration of employment is a poor measure of exposure when exposures are known to have declined over time.]

There have also been a series of studies conducted in the French stainless steel industry that involved co-exposure to several known and potential human lung carcinogens, and the most detailed exposure assessment considered nickel and chromium combined (Moulin *et al.* 1990, 1993a, b, 1995, 2000).]

The only cohort of workers exposed to metallic nickel in the absence of other nickel compounds (Oak Ridge cohort) included only 814 workers, and provided little statistical power to evaluate

lung cancer risk (Godbold & Tompkins, 1979; Cragle *et al.*, 1984).

Sorahan (2004) updated the mortality rate among employees manufacturing nickel alloys at the plant in Hereford, the United Kingdom. The study showed a significant decrease for 'all causes of death' (SMR, 0.79), for 'all cancer deaths' (SMR, 0.81), and a non-significant decrease for lung cancer (SMR, 0.87; 95%CI: 0.67–1.11).

Pang *et al.* (1996) evaluated cancer risks among 284 men who were employed for at least 3 months during 1945–75 in a nickel-plating department, and followed through 1993. For lung cancer, the overall SMR was 1.08 (95%CI: 0.54–1.94). For those with > 20 years latency, eight lung cancer deaths were observed versus 6.31 expected [SMR, 1.27; 95%CI: 0.55–2.50].

Several other studies reviewed by Sivulka (2005) had mixed exposure to metallic nickel and other nickel compounds, and provide no evidence on the carcinogenicity of metallic nickel alone. Furthermore, many of the studies cited in the review involved mixed exposures in stainless steel welding and grinding, and manufacturing nickel alloys (Cox *et al.*, 1981; Enterline & Marsh, 1982; references from Tables 5 and 6 of Sivulka, 2005), and therefore were not considered relevant for evaluating the carcinogenicity of nickel and/or nickel compounds.

2.1.2 Cancer of the nasal cavity

Increased risks for nasal cancers were found to be associated with exposures during high-temperature oxidation of nickel matte and nickel-copper matte (roasting, sintering, calcining) in cohort studies in Canada, Norway (Kristiansand), and the United Kingdom (Clydach), with exposures in electrolytic refining in a study in Norway, and with exposures during leaching of nickel-copper oxides in acidic solution (copper plant), and extraction of nickel salts from concentrated solution (hydrometallurgy) in the United Kingdom (see Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.5.pdf).

In the Norwegian study, Andersen *et al.* (1996) demonstrated a dose–response relationship between both cumulative exposure to water-soluble nickel and nickel oxide compounds and the risk of nasal cancer. The SIR (compared to the general population) was the highest in the group of workers with the highest cumulative exposure to soluble nickel compounds combined with insoluble nickel compounds (SIR, 81.7; 95%CI: 45–135; based on 15 cases). For workers with the highest cumulative exposure to nickel oxide, the SIR was 36.6 (95%CI: 19.5–62.5; based on 13 cases) (see Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.6.pdf).

An update of nasal cancer in Finnish refinery workers after 20 years since the first exposure to nickel reported an SIR of 67.1 (95%CI: 12–242.0; based on two cases) (Anttila *et al.*, 1998). An additional nasal cancer was observed 2 years after the follow-up period ended, and a fourth potential nasal cancer (classified as a nasopharyngeal cancer, 0.04 expected) was reported during the follow-up period. No nasal cancers were observed among the smelter workers who were exposed primarily to nickel matte, nickel subsulfide, nickel sulfides, and other metals.

Easton *et al.* (1992) attempted to identify the nickel compounds responsible for nasal cancer among 2524 Welsh nickel refinery workers employed for > 5 years before the end of 1969, and followed during 1931–85. As shown in Table 2.7, the risk for nasal cancer was in the range of 73–376 times the expected for those first employed before 1930, based on 67 nasal cancer deaths. A statistical model that fitted to the data on men whose exposures occurred before 1935, and that adjusted for age at first exposure, duration of exposure, and time since first exposure indicated that the soluble nickel effect on nasal cancer risk is the only one significant.

Table 2.7 Observed and expected deaths from nasal sinus cancer (1931–85) by year of first employment

Year first employed	Observed deaths	Expected deaths	SMR	95% CI
< 1920	55	0.15	376	276–477
1920–29	12	0.17	73	36–123
1930–39	1	0.07	14	0.4–80
1940–49	0	0.06	–	–
> 1950	0	0.06	–	–
Total	68	0.45	151	117–192

From Easton *et al.* (1992)

Grimsrud & Peto (2006) combined data from the most recent updates of Welsh nickel refinery workers to assess nasal cancer mortality risk by period of initial employment. For those first employed since 1930, an elevated risk was observed for nasal cancer (SMR, 8.70; 95%CI: 1.05–31.41, based on two observed deaths).

In one study of Swedish Ni–Cd battery workers, three nasal cancer cases versus 0.36 expected were observed (SIR, 8.32; 95%CI: 1.72–24.30) (Järup *et al.*, 1998). Two of these cases occurred among workers exposed to greater than 2 mg/m^3 nickel (SIR, 10.8; 95%CI: 1.31–39.0).

2.1.3 Other cancer sites

Other than for lung cancer and nasal sinus cancer, there is currently no consistency in the epidemiological data to suggest that nickel compounds cause cancer at other sites.

The results of several studies of workers exposed to nickel compounds showed a statistically elevated risk of a site-specific cancer in addition to lung and nasal cancer. A study of sinter plant workers in Canada showed a significantly elevated risk of cancer of the buccal cavity and pharynx (IARC, 1990). In a study in the Norwegian nickel-refining industry, a significant excess of laryngeal cancer was observed among roasting and smelter workers (Magnus *et al.*, 1982).

Stomach cancer was significantly elevated among men employed in a nickel- and chromium-plating factory in the United Kingdom (Burges, 1980). A study of men employed in a nickel-plating department (Pang *et al.*, 1996) showed a significant elevation in stomach cancer. Another study (Anttila *et al.*, 1998) demonstrated a significant excess of stomach cancer among nickel refinery workers.

A study of workers producing alloys with a high nickel content (Arena *et al.*, 1998) demonstrated a significant excess of colon cancer among 'non-white males' (relative risk, 1.92; 95%CI: 1.28–2.76), and a 2-fold risk of kidney cancer among white males employed in 'melting.' However, the excess risk was not associated with length of employment or time since first employment. [The Working Group noted that specific data was not provided in the article.]

A meta-analysis (Ojajärvi *et al.*, 2000) reported a significantly elevated risk for pancreatic cancer that upon further evaluation actually indicated no elevation in risk (Seilkop, 2002).

A population-based case–control study (Horn-Ross *et al.*, 1997) based on self-reported occupational exposure, showed a dose–response relationship between cumulative exposure to nickel compounds/alloys and salivary gland cancer. [The Working Group noted that the author corrected the direction of signs in Table 2 of her report in a subsequent erratum.]

2.2 Synthesis

The Working Group evaluated a large body of evidence and concluded that there is an elevated risk of lung and nasal sinus cancer among nickel refinery workers (IARC, 1990; Andersen *et al.*, 1996; Anttila *et al.*, 1998; Grimsrud & Peto, 2006), and an elevation in lung cancer risk among nickel smelter workers (IARC, 1990; Anttila *et al.*, 1998).

Epidemiological studies have provided evidence for lung cancer related to specific nickel compounds or classes of compounds (based, for example, on water solubility). Evidence for elevated risk of lung cancer in humans was demonstrated specifically for nickel chloride (Grimsrud *et al.*, 2003), nickel sulfate, water-soluble nickel compounds in general (Andersen *et al.*, 1996; Grimsrud *et al.*, 2002, 2003; Grimsrud *et al.*, 2005), insoluble nickel compounds, nickel oxides (Andersen *et al.*, 1996; Anttila *et al.*, 1998; Grimsrud *et al.*, 2003), nickel sulfides (Grimsrud *et al.*, 2002), and mostly insoluble nickel compounds (Andersen *et al.*, 1996).

A study that modelled risks of various nickel compounds and lung cancer risk identified both water-soluble nickel and metallic nickel as contributing to risk (Easton *et al.*, 1992). The largest study addressing worker exposure to metallic nickel (in combination with nickel oxide) showed a small but significant elevation in lung cancer risk (Arena *et al.*, 1998).

Other studies specifically addressing nickel metal exposures were uninformative and did not allow any judgment as to whether such exposures should be considered different with regard to cancer risk. It was not possible to entirely separate various nickel compounds in dose–response analyses for specific nickel compounds. In one analysis, an additional adjustment for water-soluble nickel compounds on risk of lung cancer indicated little association with cumulative exposure to sulfidic, oxidic or metallic nickel. One study of Ni–Cd battery workers exposed to nickel hydroxide and cadmium oxide demonstrated a significant risk of cancer of the nose and nasal sinuses.

On the basis of the Norwegian studies of refinery workers, the evidence is strongest for water-soluble nickel compounds and risk for lung cancer. The confidence of the Working Group in the above findings was reinforced by the availability of information on cigarette smoking for 89% of the Norwegian cohort, and the adjustments made for potential confounding exposures.

3. Cancer in Experimental Animals

Nickel and nickel compounds have been tested for carcinogenicity by intramuscular injection to rats, mice, and rabbits; by repository injections at multiple sites in hamsters, rabbits and mice; by intraperitoneal administration to rats and mice; and by intratracheal instillation, intrapleural, intrarenal, intraocular, inhalation, and subcutaneous exposure to rats.

Particularly relevant studies reviewed in the previous *IARC Monograph* (IARC, 1990) were reconsidered in this evaluation, and summarized in the text.

3.1 Oral administration

3.1.1 Nickel sulfide

In a 2-year multiple dose study, oral nickel sulfate hexahydrate given to male and female rats did not result in carcinogenesis (Heim *et al.*, 2007).

3.1.2 Nickel chloride

Nickel chloride was tested for carcinogenicity by oral administration in female hairless mice (CRL: SK1-hrBR). Mice were exposed to ultraviolet radiation (UVR) alone, nickel chloride alone (given in the drinking-water) and UVR + various concentrations of nickel chloride. Nickel

Table 3.1 Studies of cancer in experimental animals exposed to nickel compounds (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) 104 wk Heim *et al.* (2007)	Nickel sulfate hexahydrate 0, 10, 30, 50 mg/kg/d (gavage),[a] 60/group/sex	Keratoacanthoma (tail): M–low dose 15% (numbers not provided)	$P < 0.001$	Age at start, 6 wk 99.9% pure Exposure-related decreased bw in males and females (2 highest dose groups) Exposure-related increased mortality ($P_{trend} < 0.008$) in high dose females but not males
Mouse, CRL: Sk1-hrBR (F) 224 d Uddin *et al.* (2007)	Nickel chloride in drinking-water at 3 wk of age 3 wk later UV treatment (1.0 kJ/m²) 3 d/wk for 26 wk Groups, number of animals Group 1: Controls, 5 Group 2: UV only, 10 Group 3: 500 ppm, 10 Group 4: UV + 20 ppm, 10 Group 5: UV + 100 ppm, 10 Group 6: UV + 500 ppm, 10 5–10/group	Skin (tumours): Number of tumours/mice at 29 wk Group 1: 0 Group 2: 1.7 ± 0.4 Group 3: 0 Group 4: 2.8 ± 0.9 Group 5: 5.6 ± 0.7 Group 6: 4.2 ± 1.0	Group 5 vs Group2 $P < 0.05$ Group 6 vs Group 2 $P < 0.05$	Age at start, 3 wk Nickel had no effect on growth of the mice Nickel levels in skin increased with dose

[a] vehicle not stated

d, day or days; F, female; M, male; UVR, ultraviolet radiation; vs, versus; wk, week or weeks

chloride alone did not cause skin tumours by itself, but when combined with UVR, it increased the UVR-induced skin tumour incidence (Uddin *et al.*, 2007).

See Table 3.1.

3.2 Inhalation exposure

3.2.1 Nickel sulfate hexahydrate

Nickel sulfate hexahydrate was not shown to be carcinogenic in male or female rats or male or female mice when given by inhalation in a 2-year bioassay study (Dunnick *et al.*, 1995; NTP, 1996a). Analysis of lung burden showed that nickel was cleared from the lungs (Dunnick *et al.*, 1995).

3.2.2 Nickel subsulfide

Nickel subsulfide induced lung tumours in rats exposed by inhalation (Ottolenghi *et al.*, 1975).

Inhalation of nickel subsulfide increased the incidence of alveolar/bronchiolar adenomas and carcinomas in male F344 rats, and increased combined lung tumours in females (Dunnick *et al.*, 1995; NTP, 1996b). Nickel subsulfide also increased the incidence of adrenal pheochromocytomas (benign or malignant) in male and female rats, malignant pheochromocytomas were increased in male rats. Significant dose-related trends were observed for both lung and adrenal tumours in both sexes.

3.2.3 Nickel oxide

The carcinogenicity of nickel oxide was investigated in 2-year inhalation studies in F344 male and female rats, and B6C3F$_1$ male and female mice. Nickel oxide induced tumours of the lung (alveolar bronchiolar adenomas or carcinomas), and adrenal medulla (malignant and benign pheochromocytoma) in both sexes of rats. Nickel oxide also increased the incidence of lung tumours in low-dose females but not in male mice (NTP, 1996c).

3.2.4 Metallic nickel

Inhaled metallic nickel increased the incidence of adrenal pheochromocytomas (benign, malignant, and benign and malignant combined) in male rats and adrenal cortex tumours in female rats (Oller *et al.*, 2008). Dose-related responses were observed for both types of adrenal tumours. No significant increases in lung tumours occurred. Elevated blood levels of nickel indicated that metallic nickel was bioavailable systematically after inhalation (Oller *et al.*, 2008).

3.2.5 Other forms of nickel

Nickel carbonyl induced lung carcinomas after inhalation exposure (Sunderman *et al.*, 1957, 1959).

See Table 3.2.

3.3 Parenteral administration

3.3.1 Nickel subsulfide

(a) Mouse

Nickel subsulfide induced local sarcomas after repository injections at multiple sites in numerous studies in mice (IARC, 1990).

No increase in lung tumour incidence was observed in male strain A/J mice, 20 or 45 weeks after exposure to various treatment regimens of nickel subsulfide (McNeill *et al.*, 1990). In another study, nickel subsulfide induced injection-site tumours in all three strains of mice, with the order of susceptibility to tumour formation being C3H, B6C3F$_1$, and C57BL6 (Rodriguez *et al.*, 1996). Waalkes *et al.* (2004, 2005) studied the carcinogenic response to nickel subsulfide in MT-transgenic and MT-null mice. Intramuscular administration of nickel subsulfide increased the incidence of injections-site tumours (primarily fibrosarcoma) in MT-transgenic and concordant wild-type mice, and lung tumours in MT-transgenic mice (Waalkes *et al.*, 2004). In MT-null mice and concordant wild-type mice, intramuscular injection of nickel sulfide induced fibrosarcomas as well (Waalkes *et al.*, 2005). MT-expression, either overexpression (MT-transgenic mice) or no expression (MT-null), did not significantly affect the carcinogenic response to nickel.

(b) Rat

Nickel subsulfide induced lung tumours in rats exposed by intratracheal instillation (Pott *et al.*, 1987). Intrarenal injection resulted in dose-related increases in renal cell tumours, and intraocular injection resulted in eye tumours in rats (Jasmin & Riopelle, 1976; Sunderman *et al.*, 1979; Albert *et al.*, 1982; Sunderman, 1983). Implantation of nickel subsulfide pellets into rat heterotropic tracheal transplant caused carcinomas and sarcomas (Yarita & Nettesheim, 1978). Local tumours were also observed in rats tested by intramuscular and intrarenal injection with nickel disulfide or nickel monosulfide (crystalline but not amorphous form), and in rats tested by intramuscular injection with nickel ferrosulfide matte (Sunderman, 1984; Sunderman *et al.*, 1984).

When administered by intrarenal injection to F344 male rats, nickel subsulfide induced renal sarcomas (Kasprzak *et al.*, 1994), which showed metastases to the lung, liver, and spleen. Injection site tumours (rhabdomyosarcoma,

Table 3.2 Studies of cancer in experimental animals exposed to nickel compounds or nickel powder (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel sulfate hexahydrate				
Rat, F344 (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996a)	0, 0.125, 0.25, 0.5 mg/m^3 (equivalent to 0, 0.03, 0.06, 0.11 mg nickel/m^3) for 6 h/d, 5 d/wk 63–65/group/sex	Lung (alveolar/bronchiolar adenomas or carcinomas or squamous cell carcinomas): M–2[a]/54, 0/53, 1/53, 3/53 F[b]–0/52, 0/53, 0/53, 1/54 Adrenal medulla (pheochromocytomas, benign or malignant[c]): M–16/54, 19/53, 13/53, 12/53 F–2/52, 4/52, 3/52, 3/54		Age at start, 6 wk 22.3% Nickel No treatment-related effects on survival. Mean bw of high-dose females were slightly lower than controls. Nickel lung burden values increased with increasing exposure (at 15 mo, 0.15–1.7 µg Ni/g lung)
Mouse, B6C3F$_1$ (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996a)	0, 0.25, 0.5, 1.0 mg/m^3 (equivalent to 0, 0.06, 0.11, 0.22 mg nickel/ m^3) 6 h/d, 5 d/wk 63–65/group/sex	Lung (alveolar/bronchiolar adenomas or carcinomas): M–13/61, 18/61, 7/62, 8/61 F–7/61, 6/60, 10/60, 2/60		Age at start, 6 wk 22.3% Nickel No treatment-related effects on survival. Bw of high-dose males and all exposed female groups were decreased Nickel lung burden (µg Ni/g lung) below limit of detection at 7 and 15 mo interim evaluations

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel subsulfide				
Rat, F344 (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996b)	0, 0.15, 1 mg/m^3 (equivalent to 0, 0.11, 0.73 mg nickel/m^3) 6 h/d, 5 d/wk 63/group/sex	Lung (alveolar/bronchiolar adenomas or carcinomas or squamous cell carcinomas): M–0/53, 6/53, 11/53 F–2/53, [a]6/53, 9/53 Adrenal medulla (pheochromocytomas, benign or malignant): M–14/53, 30/53, 42/53 F–3/53, 7/53, 36/53	M: mid dose $P < 0.05$, high dose $P \leq 0.01$, $P_{trend} < 0.01$ F: mid dose $P \leq 0.05$ vs historical control, high dose $P < 0.05$, $P_{trend} < 0.05$ M: mid dose $P < 0.01$, high dose < 0.001, $P_{trend} < 0.001$ F: high dose, $P < 0.001$ $P_{trend} < 0.001$	Age at start, 6 wk 73.3% Nickel No treatment-related effects on survival. Bw in high-dose groups Nickel lung burden increased with increasing exposure but reached steady-state by 15 mo (4–7 µg Ni/g lung). Lung carcinomas also were significantly increased in high-dose males
Mouse, B6C3F$_1$ (M, F) 104 wk Dunnick *et al.* (1995), NTP 1996b	0, 0.6, 1.2 mg/m^3 (equivalent to 0, 0.44, 0.9 mg nickel/m^3) 6 h/d, 5 d/wk 63/group	Lung (alveolar/bronchiolar adenomas or carcinomas): M–13/61, 5/59, 6/58 F–9/58, 2/59, 3/60	$P = 0.038$N[h] mid dose vs control $P = 0.028$N[h] mid dose vs control $P = 0.050$N[h] high dose vs control	Age at start, 6 wk 73.3% Nickel No treatment-related effects on survival. Mean bw lower in exposed groups than control group. Nickel lung burden increased with exposure concentration and with time (at 15 mo, 12–26 µg Ni/g lung)

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) 78–80 wk + held 30 wk Ottolenghi *et al.* (1975)	Nickel subsulfide with or without 1 mo pre-exposure to the airborne system (clean air or nickel sulfide dust 0.97 ± 0.18 mg/m³ for 5 d/wk), followed by injection of hexachlorotetrafluorobutane to half the animals, thereafter the inhalation exposure was continued for all animals 16 exposure groups (8 groups/sex) Pre-exposure Inj. Controls: 29 (M), 28 (F) Inj. NiS: 29 (M), 28 (F) No Inj. Controls: 28 (M), 30 (F) No Inj. NiS: 22 (M), 26 (F) No Pre-exposure Inj. Controls: 32 (M), 32 (F) Inj. NiS: 24 (M), 32 (F) No Inj. Controls: 31 (M), 31 (F) No Inj. NiS: 32 (M), 26 (F)	Lung (adenomas, adenocarcinomas, squamous cell carcinomas, fibrosarcomas): NiS–17 (M), 12 (F) Controls–1 (M), 1 (F) Adrenal gland (hyperplasias and pheochromocytomas): NiS–12% Controls–1.1%	M, F: $P < 0.01$ $P < 0.01$	Pre-exposure: animals assigned airborne system for 1 mo No pre-exposure: animals housed in normal conditions for 1 mo Inj. = intravenous injection with pulmonary infraction agent Treatment-related decreased survival and decreased bw in males and females starting at 26 wk Inflammatory response – pneumonitis, bronchitis and emphysema Hyperplasias and squamous metaplasic changes in bronchial and bronchiolo-alveolar regions Infraction had no effect on carcinogenicity

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel oxide				
Rat, F344 (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996c)	0, 0.62, 1.25, 2.5 mg/m³ (equivalent to 0, 0.5, 1.0, 2.0 mg nickel/ m³) 6 h/d, 5 d/wk 65/group/sex	Lung (alveolar/bronchiolar adenomas or carcinomas, or squamous cell carcinomas): M–1[a]/54, 1/53, 6/53, 4/52 F–1/53, 0/53[d], 6/53, 5/54	M, F: mid dose & high dose, $P \leq 0.05$ vs high dose	Age at start, 6 wk 76.6% Nickel No treatment-related effects on survival or bw Nickel lung burden increased with exposure and with time (at 15 mo, 262–1116 µg Ni/lung)
		Adrenal medulla (pheochromocytomas, benign or malignant): M–27/54, 24/53, 27/53, 35/54 F[e]–4/51, 7/52, 6/53, 18/54	M: high dose, $P = 0.027$, $P_{trend} = 0.008$ F: high dose, $P = 0.01$, $P_{trend} < 0.001$	If the squamous cell carcinomas (lung tumours) are not included, then the mid dose and high dose are significant vs the current controls Significantly increased incidence of malignant pheochromocytomas in high-dose males
Mouse, B6C3F$_1$ (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996b)	0, 1.25, 2.5, 5.0 mg/m³ (equivalent to 0, 1.0, 2.0, 3.9 mg nickel/m³) 6 h/d, 5 d/wk ≈80/group/sex	Lung (alveolar/bronchiolar adenomas or carcinomas): M–9/57, 14/67, 15/66, 14/69 F–6/64, 15/66, 12/63, 8/64	F: low dose, $P \leq 0.01$	Age at start, 6 wk; 76.6% Nickel No treatment-related effects on survival or bw Nickel lung burden increased with exposure and with time (at 15 mo, 331–2258 µg Ni/lung)

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel metal powder				
Rat, Wistar Crl:Wi (G1XBRl/Han) (M, F) 12–30 mo Oller *et al.* (2008)	0, 0.1, 0.4, 1 mg/m^3 for 6 h/d, 5 d/wk, exposure time, additional hold time– Group 1: 0, 24 mo, 6 mo Group 2: 0.1, 24 mo, 6 mo Group 3, F: 0.4, 19 mo, 11 mo Group 3, M: 0.4, 24 mo, 6 mo Group 4, F: 1.0, ~14 mo, 0 mo Group 4, M: 1.0, ~12 mo, 0 mo 50/group	Groups 1, 2, 3 Adrenal gland (pheochromocytomas, benign or malignant): M–0/50, 5/50, 21/50 F–0/50, 5/49, 3/53 Adrenal cortex (adenomas or carcinomas): M–1/50, 3/50, 2/50 F–2/50, 2/49, 7/54	M: 0.4 mg/m^3 Significant increase for benign, malignant, benign combined, significant dose-related response[f] F: 0.4 mg/m^3 Significant increase for combined (adenoma and carcinoma) and significant dose-related response[f]	Age at start, 6 wk 99.9% pure Exposure-related mortality was observed in the high-dose group (Group 4 M, F, these animals were removed from the main study), and in Group 3 F (animals from satellite study reassigned to main study). Exposure-related bw effects were observed in Groups 2 (M), 3 (F &M), and 4 (F &M). Exposure-related lung toxicity was observed. Nickel lung burden (µg Ni/lung) increased with exposure and with time (appeared to reach steady-state at 12 mo)[g]. Increases in adrenal tumours were within published (external) historical controls for Wistar rats

[a] Includes 1 squamous cell carcinoma
[b] Only alveolar bronchiolar adenomas observed in female rats; adjusted rate not reported
[c] Adjusted rates not provided
[d] Dunnick reported 1 tumour and NTP technical report reported 0
[e] Only benign tumours observed.
[f] *P*-value not reported calculated by Peto
[g] Data not available for all time points
[h] A negative trend or a lower incidence in an exposure group is indicated by N
bw, body weight; d, day or days; h, hour or hours; F, female; M male; mo, month or months; Ni, nickel; NR, not reported; vs, versus; wk, week or weeks

fibromas, malignant fibrous histiocytomas or leiomyosarcomas) were observed in male or female F344 rats administered nickel subsulfide intramuscularly (Ohmori *et al.*, 1990; Kasprzak & Ward, 1991), and intra-articularly (Ohmori *et al.*, 1990). One study found that in female rats subjected to bone fractures and treated intramuscularly or intra-articularly had a shorter time to sarcoma formation, reduced survival time, and higher metastatic rate than rats treated with nickel alone (Ohmori *et al.*, 1990). Ohmori *et al.* (1999) studied strain susceptibility in male and female Wistar rats, and one strain (CRW) was found to be more sensitive to intramuscular injection of nickel.

(c) Hamster

Nickel subsulfide induced local sarcomas after repository injections at multiple sites in numerous studies in hamsters (IARC, 1990).

(d) Rabbit

Nickel subsulfide induced local sarcomas after repository injections at multiple sites in numerous studies rabbits (IARC, 1990).

3.3.2 Nickel oxide and hydroxide

Nickel oxide induced lung tumours in rats by intratracheal instillation (Pott *et al.*, 1987), local sarcomas in mice by intramuscular injection (Gilman, 1962), and rats by intramuscular, intrapleural, and intraperitoneal injection (Gilman, 1962; Sunderman & McCully, 1983; Skaug *et al.*, 1985; Pott *et al.*, 1987). Nickel hydroxide induced local sarcomas in rats when tested by intramuscular injection (Gilman, 1966; Kasprzak *et al.*, 1983).

Sunderman *et al.* (1990) tested the carcinogenicity of five nickel oxides or nickel-copper oxides in male Fisher 344 rats. The three oxides that induced sarcomas at the injection sites had measurable dissolution rates in body fluids, and were strongly positive in an erythrocytosis stimulation assay, demonstrating nickel bioavailability.

3.3.3 Nickel acetate

(a) Mouse

Nickel acetate when administered by intraperitoneal injection induced lung adenocarcinomas and pulmonary adenomas in Strain A mice (Stoner *et al.*, 1976; Poirier *et al.*, 1984).

(b) Rat

Nickel acetate induced malignant tumours in the peritoneal cavity when administered by intraperitoneal injection in rats (Pott *et al.*, 1989, 1990).

A single intraperitoneal injection of nickel acetate initiated renal epithelial tumours (including carcinoma) after promotion using sodium barbital in the drinking-water in male rats (Kasprzak *et al.*, 1990).

See Table 3.3.

3.3.4 Metallic nickel

Intratracheal administration of metallic nickel powder caused lung tumours in rats (Pott *et al.*, 1987). Metallic nickel also caused local tumours in rats when administered by injection (intrapleural, subcutaneous, intramuscular, and intraperitoneal) (Hueper, 1952, 1955; Mitchell *et al.*, 1960; Heath & Daniel, 1964; Furst & Schlauder, 1971; Berry *et al.*, 1984; Sunderman, 1984; Judde *et al.*, 1987; Pott *et al.*, 1987, 1990).

3.3.5 Nickel sulfate

Nickel sulfate induced malignant tumours in the peritoneal cavity when administered by intraperitoneal injection in rats (Pott *et al.*, 1989, 1990).

Table 3.3 Studies of cancer in experimental animals exposed to nickel compounds (parenteral administration and intratracheal instillation)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel subsulfide				
Mouse, Strain A (M) 45 wk McNeill *et al.* (1990)	i.t. and i.p. 0, 0.53, 0.160 mg/kg bw 3 dosing regimens for 15 wk 1/wk (15 treatments), 1 every 2 wk (8 treatments), 1 every 3 wk (5 treatments); 3 doses per regiment; 30/group 10 mice sacrified after 20 wk	Lung (adenomas at 45 wk[a]): i.t.– Number of treatments: dose 5: 68%, 63%, 58% 8: 64%, 54%, 61% 15: 47%, 47%, 56% i.p.– 5: 68%, 63%, 53% 8: 58%, 53%, 63% 15: 63%, 47%, 50%		Age at start, 8–10 wk Nickel subsulfide –1.8 µm mass medium diameter 73% Nickel and 26.3% sulfur (weight) Urethane (positive control) significantly increased tumour incidence i.p., i.t., after 20 wk, and i.t. after 45 wk, average. number of adenoma/mouse increased i.p. and i.t. at both time points No treatment effects on bw
Mouse, C57BL/6, B6C3F$_1$, CeH/He (M) 78 wk Rodriguez *et al.* (1996)	i.m. (thigh) 0, 0.5, 1.0, 2.5, 5.0, 10 mg/site (single injection) 30/group	Injection site (rhabdomyosarcomas, fibrosarcomas, and other e.g. liposarcomas, haemangiosarcomas): C3He 0/30, 5/30 (16.6%), 10/30 (33.3%), 20/27 (74.1%), 28/29, (96.6%) 14/14 (100%) B6C3F$_1$ 0/30, 2/29 (6.9%), 8/30 (26.7%), 15/30 (50.0%), 16/20 (80%), 5/6 (83.3%) C57BL 0/24, 1/27 (3,7%), 4/28 (14.3%), 6/21 (28.6%), 6/15(40%), 0/2	[$P = 0.052$, 0.5 mg; $P < 0.001$ for other doses][a] [$P < 0.01$, 1.0 mg, $P < 0.001$, 2.5, 5.0, 10 mg][a] [$P < 0.01$, 2.5, 5 mg][a]	Age at start, 6–8 wk; weight, 23–29 g High dose was lethal within 1 wk to over 50% of all 3 strains; susceptibility was C57BL > B6C3F1 > C3H Treatment-related decrease in bw was observed for C3H and B6C3F$_1$ at 2 highest doses. Tumours of the liver, lung adenomas and leukaemias were also observed, but were not increased in exposed groups compared to controls Susceptibility to tumours C3H > B6C3F$_1$ > C57BL

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, MT transgenic and wild-type (M) 104 wk Waalkes *et al.* (2004)	i.m. (both thighs) 0, 0.5, 1 mg/site (single injection) 25/group	Injection site (primarily fibrosarcomas, but also included fibromas and lymphosarcomas): WT–0/24, 5/25 (20%), 10/25 (40%) MT-Tg–0/25, 7/25 (28%), 7/24 (29%) Lung (adenomas or adenocarcinomas): WT–6/24 (25%), 5/25 (20%), 9/25 (36%) MT-Tg–0/25, 3/25 (12%), 4/24 (17%)	WT: $P < 0.05$, mid-and low dose, $P_{trend} < 0.0001$ MT-Tg: $P < 0.05$, mid-and low dose, $P_{trend} = 0.0081$ trend MT-Tg: $P = 0.0502$ high dose $P_{trend} = 0.046$	Age at start, 12 wk 99.9% pure, 30 µm particles Average survival time less in MT-Tg mice than controls. Treatment-related decrease in survival in WT but not MT-Tg mice. No effect on bw No differences in injection-site tumour incidence or latency between MT-Tg and WT mice MT-transgenic controls had significantly lower incidence of lung tumours than WT controls.
Mouse, MT-null (double knockout) and wild-type (M) 104 wk Waalkes *et al.* (2005)	i.m. (both thighs) 0, 0.5, 1 mg/site (single injection), 25/group	Injection site (primarily fibrosarcomas, but also included fibromas): WT–0/24, 8/25(32.0%), 18/25 (72.0%) MT-null–0/24, 11/24 (45.8%), 15/23 (62.5%) Lung (adenomas or adenocarcinomas): WT–7/24 (29.2%), 12/25 (48.0%), 11/25 (44.0%) MT-null–10/24 (41.7%), 13/24 (54.2%), 4/23 (16.7%)	$P < 0.05$ low and high dose $P < 0.05$ low and high dose	Age at start, 12 wk 99.9% pure, < 30 µm particles No difference in survival between control MT-null mice and control WT mice. Nickel treatment reduced survival at later time points corresponding to the appearance of sarcomas. Nickel treatment reduced bw in high-and mid dose MT-null and high-dose WT mice

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, MT-null (double knockout) and wild-type (M) 104 wk Waalkes *et al.* (2005) (contd.)		Lung (adenocarcinomas): WT–1/24 (4.2%), 10/25 (40.0%), 3/25 (12.0%) MT-null–3/24 (12.5%), 3/24 (12.5%), 4/23 (17.4%) Lung (adenomas): WT–6/24 (25%), 2/25 (8.0%), 8/25 (32.0%) MT-null–7/24 (29.2%), 10/24 (41.7%), 0/23	WT: $P < 0.05$ low dose MT-null: $P < 0.05$ control vs high dose	
Rat, F344/NCr (M) 109 wk Kasprzak *et al.* (1994)	i.r. (2 injections) Ni_3S_2 – 5 mg, MgCarb –6.2 mg, Fe^0–3.4 mg Groups: treatment, number of animals Group 1: Ni_3S_2, 40 Group 2: Ni_3S_2 + MgCarb, 20 Group 3: MgCarb, 20 Group 4: Ni_3S_2+ Fe^0, 20 Group 5: Fe^0, 20 Group 6: vehicle, 20 20–40/group	Kidney (malignant tumours of mesenchymal cell origin) at 104 wk: Group 1: 25/40 (63%) Group 2: 4/20 (20%) Group 3: 0/20 Group 4: 12/20 (60%) Group 5: 0/20 Group 6: 0/20	Group 2 vs Group 1 [$P < 0.01$][a]	Ni_3S_2 < 10µm No effect on bw or survival (from causes other than kidney tumours) MgCarb also delayed onset of tumours (besides decreasing the incidence), and Fe decreased time until first tumour Metastases to lung, liver, spleen and other kidney

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344/NCr (M) 109 wk Kasprzak & Ward (1991)	i.m. and s.c (single injection) Ni_3S_2 – 2.5 mg, MB – 0.5 mg, CORT–1.0 mg, IND –1.0 mg. Groups: i.m., s.c., number of animals Group 1: Ni_3S_2, none, 20 Group 2: MB, none, 20 Group 3: Ni_3S_2+ MB, none, 20 Group 4: CORT, none, 20 Group 5: Ni_3S_2+ CORT, none, 20 Group 6: IND, none, 20 Group 7: Ni_3S_2+ IND, none, 20 Group 8: water, none, 20 Group 9: Ni_3S_2, MB, 20 Group 10: Ni_3S_2, IND, 20 20/group	Injection-site tumours (rhabdomosarcomas, fibrosarcomas, histolytic sarcomas): 36 wk; 71 wk Group 1: 10/20 (50%); 17/20 (85%) Group 2: 0/20; 0/20 Group 3:0/20; 1/20 (5%) Group 4: 0/20; 0/20 Group 5: 9/20 (45%); 17/20 (85%) Group 6: 0/20; 0/20 Group 7: 6/20 (30%); 16/20 (80%) Group 8: 0/20; 0/20 Group 9: 18/20 (90%); 20/20 (100%) Group 10: 13/20 (65%); 19/20 (95%)	[Groups 2, 3, 4, 6 or 8 vs Group 1, 36 & 71 wk, $P < 0.01$; Group 9 vs Group 1, 36 wk, $P < 0.05$][a]	Age at start, 8 wk Ni_3S_2 < 10µm No effect on bw Metastases to the lung MB given away from the injection site (s.c.) decreased tumour latency induced by Ni_3S

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (F) 1 yr Ohmori *et. al.* (1990)	Ni_3S_2–10 mg Groups, treatment, number of animals Group 1: fracture bone, 10 mg/fracture, 20 Group 2: 10 mg i.m right thigh, 20 Group 3: 10 mg i.a. right knee joint, 20 Group 4: control (CM), 3 fractured bone, 3 i.m., 2 i.a. 20/group	Injection site (malignant fibrous histiocytomas, rhabdomyosarcomas, fibrosarcomas, leiomyosarcomas): Group 1: 17/20 (85%) Group 2: 20/20 (100%) Group 3: 16/20 (80%) Group 4: 0/7 (0%) Metastasis (lymph node, lung): Group 1: 16/17 (94.1), 9/17 (52.9) Group 2: 5/20 (25.0%), 3/20 (15.0%) Group 3: 3/16 (18.8%), 2/16 (12.5%) Group 4: 0/7, 0/7	$P < 0.05$, Group 1 vs Group 2 or Group 3	Age at start, 10 wk Ni_3S_2 medium particle diameter < 2μm Vehicle, CM Tumour-induction time and survival time shorter in Group 1 than Groups 2 or 3. No osteogenic sarcoma developed in bone-fracture group
Rat, Wistar (M, F) 70 wk Ohmori *et al.* (1999)	Ni_3S_2–10 mg i.m. (single injection) Groups, strain, treatment; number of animals Group 1: SHR–10 mg; 15F, 15M Group 2: CWR–10 mg; 15F, 16M Group 3: SHR–0 mg; 6F, 6M Group 4: CWR–0 mg 7F, 7M 6–15/group	Sarcomas (rhabdomyosarcomas, leiomyosarcomas, fibrosarcomas and malignant fibrous histiocytomas): Groups: F; M; Total Group 1: 2/15 (13.3%); 5/15 (33.3%); 7/30 (23.3%) Group 2: 8/15 (53.3%), 13/16 (81.4%); 21/31 (67.7%) Group 3: 0/6, 0/6 Group 4: 0/7, 0/7	Total: Group 1 vs Group 2, $P < 0.005$	Age, 10 wk Ni_3S_2 medium particle diameter < 2μm Vehicle, CM Tumour incidence, progression (as shown by tumour size and metastasis) was significantly lower in SHR rats (M, F combined) than in CWR rats Metastases observed in the lung and lymph node

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel oxide				
Rat, F344 (M) 104 wk Sunderman *et al.* (1990)	i.m. (hind limb) single injection Group: Ni by wt.; other elements V: vehicle control (glycerol) A: 0.81% Ni (III); none B: 0.05% Ni (III); none F: < 0.03% Ni (III); none H: 21% Cu, 2% Fe, 1.1% Co, 1% S, 0.5% Ni_3S_2 I: 13% Cu, 1.2% Fe, 1.0 Co, 0.3% S, 1.0% Ni_3S_2 (positive control) 20 mg Ni/rat 15/group	Injection site (rhabdomyosarcomas, fibrosarcomas, malignant fibrous histiocytomas, leiomyosarcomas, undifferentiated): V, 0/15; A, 6/15 (40.0%); B, 0/15; F, 0/15; H, 13/15 (86.7%); I, 15/15 (100%) Positive control, Ni_3S_2 15/15(100%) **Metastases** V: 0, A: 3; B: 0; F: 0; H: 4; I: 4 Ni_3S_2: 12 **Other primary tumours** V: 0; A: 0; B: 3; F: 0; H: 0; I: 3 Ni_3S_2: 0	$P < 0.01$ A; $P < 0.001$ H, I, Ni_3S_2	Age at start, ~2 mo 5 NiO compounds – all compounds had 52–79% Nickel (total), and 22–24% O. Nickel could not be determined in Groups H and I because of the presence of sulfur Groups A, H, and I all had measurable dissolution rates in body fluids and were strongly positive in an erythrocytosis-stimulation assay Compounds B and F were insoluble in body fluids, did not stimulate erythrocytosis and had little Ni (III), Cu Fe, Co, or S
Rat, Wistar (F) Life span Pott *et al.* (1987)	(mg x wk) number of animals NiO 50 mg (10 × 5); 34 150 mg (10 × 15); 37 Ni_3S_2 0.94 mg (15 × 0.063); 47 1.88 mg (15 × 0.125); 45 3.75 mg (15 × 0.25); 47 Nickel powder 6 mg (20 × 0.3); 32 9 mg (10 × 0.9); 32 32–47/group	Lung (adenomas, adenocarcinomas, squamous cell carcinomas): % tumours for each dose NiO–27%, 31.6% Ni_3S_2–15%, 28.9% Nickel powder–25.6%, 25% Saline, 0%		Age at start, 11 wk NiO, 99.9% pure

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel acetate				
Rat, F344/NCr (M) 101 wk Kasprzak *et al.* (1990)	NiAcet –90 µmol/kg bw single i.p. injection NaBB–50 ppm in drinking-water (2 wk after NiAcet) Groups, treatment, # of animals Group 1: NiAcet, 23 Group 2: NiAcet + NaBB, 24 Group 3: NaBB, 24 Group 4: Saline, 24 24/group	Renal cortical tumours (adenomas & adenocarcinomas): Group 1–1/23 (4.3%) Group 2–16/24 (66.7%) (4 carcinomas) Group 3–6/24 (25%) Group 4–0/24 Renal pelvic tumours (papillomas & carcinomas): Group 1–0/23 Group 2–8/24 (33.3%) Group 3–13/24 (54.2%) (1 carcinoma) Group 4–0/24	$P < 0.008$ vs Group 3	Age at start, 5 wk Initiation/promotion study Decreased survival and bw in rats given nickel acetate followed by NaBB Kidney weight increased in Groups 2 and 3 Renal cortical tumours: metastatic nodules observed in the lung, spleen and liver
Mouse, Strain A (M, F) 30 wk Stoner *et al.* (1976)	i.p. Nickel acetate 3×/wk (24 injections total) 0, 72, 180, 360 mg/kg Saline control 20/group	Lung (adenomas): Average number of tumours/mouse (mean ± SD) Saline: 0.42 ± 0.10 72: 0.67 ± 0.16 180: 0.71 ± 0.19 360: 1.26 ± 0.29	$P < 0.01$ high dose	Age at start, 6–8 wk 99.9% pure Sample of nodules confirmed by histopathology No difference in control M, F, so M, F were combined Positive control urethane Control saline Doses correspond to MTD, ½ MTD, 1/5 MTD
Mouse, Strain A (M, F) 30 wk Poirier *et al.* (1984)	i.p. Nickel acetate 10.7 mg/kg bw (0.04 mmol kg/bw)/injection 3×/wk (24 injections total) 30/group/sex	Lung (adenomas): Average number of tumours/mouse (mean ± SD) Saline: 0.32 ± 0.12 Nickel acetate: 1.50 ± 0.46	$P < 0.05$	Age at start, 6–8 wk Nodules (sample) confirmed by histology Co-exposure to calcium and magnesium decreased multiplicity

[a] Calculated by Fisher Exact Test, Significance not reported by authors

bw, body weight; CM, chloromycetin; CORT, cortisol; CWR, common closed colony rats; F, female; Fe^0, metallic iron; HSR, spontaneously hypertensive rats; i.a., intra-articular; i.f., intra-fat; i.m., intramuscular; IND, indometacin; i.p., intraperitoneal; i.r., intrarenal; i.t., intratracheal instillation; M, male; MB, *Mycobacterium bovis* antigen; MgCarb, magnesium basic carbonate; MT, metallothionien; MTD, maximum tolerated dose; NABB, sodium barbital; Ni, nickel; NiAcet, nickel acetate; Ni_3S, nickel subsulfide; s.c., subcutaneous; SD, standard deviation; Tg, Transgenic; wk, week or weeks; WT, wild type; yr, year or years

Table 3.4 Studies of cancer in experimental animals exposed to nickel acetate (transplacental exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Results Target organs	Significance	Comments
Rat, F344/NCr (M, F) 85 wk Diwan *et al.* (1992)	*Dams – i.p* NiAcet (90 µmol/kg wt total) Group:/µmol/kg bw; regimen Group 1: 90; once at Day 17 of gestation Group 2: 45; twice at Days 16 & 18 of gestation Group 3: 45; 4 times at Days 12, 14, 16, 18 of gestation Group 4: control (180 NaAcet) once at Day 18 of gestation *Offspring 4 to 85 wk (drinking-water)* ad libitum 1A, 2A, 4A – tap water 1B, 2B, 4B – 0.05% NBB	Renal tumours (cortex adenomas and carcinomas; or pelvis papillomas and carcinomas): 1A: 0/17 (M), 0/16 (F) 2A: 0/15 (M), 0/15 (F) 4A: 0/15 (M), 0/16 (F) 1B: 8/15 (53.3%, M), 0/15 (F) 2B: 7/15 (46.7%, M), 0/15 (F) 4B: 1/15 (6.67%, M), 0/14 (F) Pituitary gland (adenomas or carcinomas): 1A: 9/17 (52.9%, M), 5/16 (31.3%, F), 14/33 (42.3%, M, F) 2A: 6/15 (40.0%, M), 8/16 (50%, F), 14/31 (45.2%, M, F) 4A: 1/15 (6.7%, M), 3/14 (21.4%, F) 1B: 6/15 (40.0%, M), 5/15 (33.3%, F) 2B: 7/15 (46.7%, M), 6/15 (40.0%, F) 4B: 2/15 (13.3%, M), 4/14 (28.6%, F)	M: $P = 0.007$ (1B vs 4B) M: $P = 0.012$ (2B vs 4B) M, F: $P = 0.12$ 1A vs 4A M, F: $P = 0.008$ 2A vs 4A	Dams, age at start 3–4 mo Purity not provided Male (Groups 1 & 2) – significantly decreased bw at 75 wk All offspring in Group 3 died at 72 h. Survival was decreased in Groups 1A, 1B, 2A and 2B compared to controls (4A and 4B) Pituitary tumours: significantly decreased latency for Groups 1A (M, F), 1B (M, F) and 2A (F) compared to the Groups 4A or 4B (corresponding M or F)

h, hour or hours; F, female; i.p., intraperitoneal; M, male; mo, month or months; NaBB, sodium barbital; vs, versus; wk, week or weeks

3.3.6 Nickel chloride

Nickel chloride induced malignant tumours in the peritoneal cavity when administered by intraperitoneal injection in rats (Pott *et al.*, 1989, 1990).

3.3.7 Other forms of nickel

Intramuscular administration of nickel sulfarsenide, nickel arsenides, nickel antimonide, nickel telluride, and nickel selenides caused local sarcomas in rats (Sunderman & McCully, 1983). Intramuscular administration of nickelocene caused some local tumours in rats and hamsters (Furst & Schlauder, 1971).

3.4 Transplacental exposure

3.4.1 Nickel acetate

Diwan *et al.* (1992) studied the carcinogenic effects of rats exposed transplacentally to nickel acetate and postnatally to sodium barbital in drinking-water. Pregnant F344 were given nickel acetate by intraperitoneal injection, and their offspring were divided into groups receiving either tap water or sodium barbital in drinking-water. An increased incidence in pituitary tumours was observed in the offspring of both sexes transplacentally exposed to nickel acetate. These tumours were mainly malignant, and are rare tumours. Renal tumours were observed in the male offspring exposed transplacentally to nickel acetate, and receiving sodium barbital postnatally, but not in the male offspring receiving tap water after nickel *in utero*.

See Table 3.4.

3.5 Synthesis

The inhalation of nickel oxide, nickel subsulfide, and nickel carbonyl caused lung tumours in rats. Intratracheal instillation of nickel oxide, nickel subsulfide, and metallic nickel caused lung tumours in rats. Lung tumours were observed by the intraperitoneal injection of nickel acetate in two studies in A/J mice, and by intramuscular injection of nickel subsulfide in mice. The inhalation of nickel oxide, nickel subsulfide, and metallic nickel caused adrenal medulla pheochomocytoma in rats. Transplacental nickel acetate induced malignant pituitary tumours in the offspring in rats. Several nickel compounds (nickel oxides, nickel sulfides, including nickel subsulfide, nickel sulfate, nickel chloride, nickel acetate, nickel sulfarsenide, nickel arsenide, nickel antimonide, nickel telluride, nickel selenide, nickelocene, and metallic nickel) administered by repository injection caused sarcomas in multiple studies. The inhalation of metallic nickel did not cause lung tumours in rats. The inhalation and oral exposure to nickel sulfate did not cause tumours in rats or mice. The inhalation of nickel subsulfite did not cause tumours in mice.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

In rodents, nickel salts and nickel sulfides are absorbed through the lungs and excreted mainly in the urine (Benson *et al.*, 1994, 1995a). After inhalation exposure to green nickel oxide, nickel is not distributed in extrapulmonary tissues, and is excreted only in faeces (Benson *et al.*, 1994). In humans, soluble nickel compounds are rapidly absorbed through the lungs, and excreted in the urine. After inhalation exposure to insoluble nickel species, elevated concentrations of nickel are observed in the plasma and urine, but the absorption is slow (Bernacki *et al.*, 1978; Tola *et al.*, 1979).

In rats exposed to nickel sulfate hexahydrate by inhalation for 6 months or 2 years,

no pulmonary accumulation is observed; in a similar exposure scenario with nickel subsulfide, concentrations of nickel are detected in the lungs, with very slight nickel accumulation. Following the exposure of green nickel oxide to rats, the nickel lung clearance half-life is approximately 130 days, and in long-term exposure (NTP, 1996a, b, c; described in Section 3), a remarkable accumulation of nickel is observed (Benson *et al.*, 1995b; Dunnick *et al.*, 1995). The lung clearance half-life of nanoparticulate black nickel oxide in rats is reported as 62 days (Oyabu *et al.*, 2007). The difference in the two clearance rates may be related to the greater water solubility (and the smaller particle size) of the nanoparticulate black nickel oxide. In mice, the observed clearance for nickel sulfate is fast, but for nickel subsulfide intermediate and for green nickel oxide, very slow (Dunnick *et al.*, 1995).

4.1.1 Cellular uptake

Nickel chloride has been shown in different cell lines in culture to be transported to the nucleus (Abbracchio *et al.*, 1982; Edwards *et al.*, 1998; Ke *et al.*, 2006, 2007; Schwerdtle & Hartwig, 2006). Soluble nickel chloride compounds enter cells via the calcium channels and by metal ion transporter 1 (Refsvik & Andreassen, 1995; Funakoshi *et al.*, 1997; Gunshin *et al.*, 1997; Garrick *et al.*, 2006). Crystalline nickel sulfides are phagocytized by a large variety of different cells in culture (Kuehn *et al.*, 1982; Miura *et al.*, 1989; Hildebrand *et al.*, 1990, 1991; IARC, 1990).

Black nickel oxide and nickel chloride are taken up by human lung carcinoma cell lines A549 in culture; the nucleus/cytoplasm ratio is > 0.5 for black nickel oxide, and < 0.18 for nickel chloride (Fletcher *et al.*, 1994; Schwerdtle & Hartwig, 2006).

After phagocytosis of nickel subsulfide, intracellular nickel containing particles rapidly dissolve, and lose sulfur (Arrouijal *et al.*, 1990; Hildebrand *et al.*, 1990, 1991; Shirali *et al.*, 1991).

4.2 Genetic and related effects

The mechanisms of the carcinogenicity of nickel compounds have been reviewed extensively (Hartwig *et al.*, 2002; Zoroddu *et al.*, 2002; Costa *et al.*, 2003, 2005; Harris & Shi, 2003; Kasprzak *et al.*, 2003; Lu *et al.*, 2005; Durham & Snow, 2006; Beyersmann & Hartwig, 2008; Salnikow & Zhitkovich, 2008).

Based on the uptake and distribution in cells described above, the ultimate genotoxic agent is Ni (II). However, direct reaction of Ni (II) with DNA does not seem to be relevant under realistic exposure conditions. Nevertheless, nickel is a redox-active metal that may, in principle, catalyse Fenton-type reactions, and thus generate reactive oxygen species (Nackerdien *et al.*, 1991; Kawanishi *et al.*, 2001). Genotoxic effects have been consistently observed in exposed humans, in experimental animals, and in cell culture systems, and include oxidative DNA damage, chromosomal damage, and weak mutagenicity in mammalian cells. These effects are likely to be due to indirect mechanisms, as described in detail below.

4.2.1 Direct genotoxicity

(a) DNA damage

Water-soluble as well as water-insoluble nickel compounds induce DNA strand breaks and DNA protein crosslinks in different mammalian test systems, including human lymphocytes. Nevertheless, in the case of DNA strand breaks and oxidative DNA lesions, these events mainly occur with conditions that involve comparatively high cytotoxic concentrations (IARC, 1990; Pool-Zobel *et al.*, 1994; Dally & Hartwig, 1997; Cai & Zhuang, 1999; Chen *et al.*, 2003; M'Bemba-Meka *et al.*, 2005; Schwerdtle & Hartwig, 2006; Caicedo *et al.*, 2007). This is also true for the induction of oxidative DNA base modifications in cellular systems. Nevertheless, oxidative DNA damage is also observed in experimental animals, this may

be due to repair inhibition of endogenous oxidative DNA damage.

The intratracheal instillation of several soluble and insoluble nickel compounds to rats significantly increases 8-hydroxydeoxyguanine (8-OH-dG) content in the lungs. Concomitantly, microscopic signs of inflammation in the lungs are also observed. Two distinct mechanisms are proposed: one via an inflammatory reaction and the other through cell-mediated reactive oxygen species formation (Kawanishi *et al.*, 2001; Kawanishi *et al.*, 2002).

(b) Chromosomal alterations

Water-soluble and poorly water-soluble nickel compounds induce sister chromatid exchange and chromosomal aberrations at toxic levels in different mammalian test systems (Conway *et al.*, 1987; Conway & Costa, 1989; IARC, 1990; Howard *et al.*, 1991). Chromosomal aberrations are most pronounced in heterochromatic chromosomal regions (Conway *et al.*, 1987). Water-soluble and poorly water-soluble nickel compounds induce micronuclei at comparatively high concentrations. Because increases in both kinetochore-positive and -negative micronuclei are observed, these effects are likely due to aneugenic as well as clastogenic actions (Arrouijal *et al.*, 1990, 1992; Hong *et al.*, 1997; Seoane & Dulout, 2001). The induction of chromosomal aberrations and micronuclei in rodents treated with different nickel compounds is not consistent across studies (Sobti & Gill, 1989; Arrouijal *et al.*, 1990; Dhir *et al.*, 1991; IARC, 1990; Oller & Erexson, 2007). Enhanced frequencies of chromosomal aberrations were observed in some studies in lymphocytes of nickel-exposed workers (IARC, 1990).

(c) Gene mutations in bacterial and mammalian test systems

Nickel compounds are not mutagenic in bacterial test systems, and are only weakly mutagenic in cultured mammalian cells. Even though, mutagenic responses for both water-soluble and water-insoluble nickel compounds have been reported in transgenic G12 cells, this effect was later shown to result from epigenetic gene-silencing (Lee *et al.*, 1995). Nevertheless, the prolonged culture of V79 cells after treatment with nickel sulfate results in the appearance of genetically unstable clones with high mutation rates together with chromosomal instability (Little *et al.*, 1988; Ohshima, 2003).

(d) Cell transformation

Water-soluble and poorly water-soluble nickel compounds induced anchorage-independent growth in different cell systems (IARC, 1990), including the mouse-embryo fibroblast cell-line PW and the human osteoblast cell line HOS-TE85 (Zhang *et al.*, 2003). Nickel compounds were shown to cause morphological transformation in different cell types (Conway & Costa, 1989; Miura *et al.*, 1989; Patierno *et al.*, 1993; Lin & Costa, 1994).

4.2.2 Indirect effects related to genotoxicity

As stated above, the direct interaction of nickel compounds with DNA appears to be of minor importance for inducing a carcinogenic response. However, several indirect mechanisms have been identified, which are discussed below.

(a) Oxidative stress

Treatment with soluble and insoluble nickel causes increases in reactive oxygen species in many cell types (Huang *et al.*, 1993; Salnikow *et al.*, 2000; Chen *et al.*, 2003).

Increased DNA stand breaks, DNA–protein crosslinks and sister chromatid exchange are found in cells treated with soluble and insoluble nickel compounds, and these are shown to result from the increase in reactive oxygen species (Chakrabarti *et al.*, 2001; Błasiak *et al.*, 2002; Woźniak & Błasiak, 2002; M'Bemba-Meka *et al.*, 2005, 2007).

Intraperitoneal injection of nickel acetate in rat did not cause any DNA damage in liver and kidney at 12 hours. However, oxidative DNA damage increased after 24 hours, and persisted in the kidney for 14 days (Kasprzak *et al.*, 1997).

(b) Inhibition of DNA repair

The treatment of cells with soluble Ni (II) increases the DNA damage and the mutagenicity of various agents (Hartwig & Beyersmann, 1989; Snyder *et al.*, 1989; Lee-Chen *et al.*, 1993).

Soluble Ni (II) inhibits nucleotide-excision repair after UV irradiation, and the effect seems to be on the incision, the polymerization, and ligation steps in this pathway (Hartwig *et al.*, 1994; Hartmann & Hartwig, 1998; Woźniak & Błasiak, 2004). One of the proteins in nucleotide-excision repair, the XPA protein, may be a target of Ni (II) (Asmuss *et al.*, 2000a, b).

Soluble nickel chloride also inhibits base-excision repair. The base-excision repair enzyme, 3-methyladenine-DNA glycosylase II, is inhibited specifically (Dally & Hartwig, 1997; Woźniak & Błasiak, 2004; Wang *et al.*, 2006).

There is some evidence that the enzyme O^6-methylguanine-DNA methyltransferase (MGMT) is inhibited by nickel chloride (Iwitzki *et al.*, 1998).

(c) Epigenetic mechanisms

Both water-soluble and water-insoluble nickel compounds are able to cause gene silencing (Costa *et al.*, 2005). This effect was first found when "mutations" in the transgenic *gpt* gene in G12 cells were found to be epigenetically silenced rather than mutated (Lee *et al.*, 1995). Genes that are located near heterochromatin are subject to such inactivation by nickel. The *gpt* gene was silenced by DNA methylation. Additional studies show that cells treated with nickel have decreased histone acetylation, and altered histone methylation patterns (Golebiowski & Kasprzak, 2005; Chen *et al.*, 2006). Nickel also causes ubiquination and phosphorylation of histones (Karaczyn *et al.*, 2006; Ke *et al.*, 2008a, b). Permanent changes in gene expression are important in any mechanism of carcinogenesis.

4.3 Synthesis

The ultimate carcinogenic species in nickel carcinogenesis is the nickel ion Ni (II). Both water-soluble and poorly water-soluble nickel species are taken up by cells, the former by ion channels and transporters, the latter by phagocytosis. In the case of particulate compounds, nickel ions are gradually released after phagocytosis. Both water-soluble and -insoluble nickel compounds result in an increase in nickel ions in the cytoplasm and the nucleus. Nickel compounds are not mutagenic in bacteria, and only weakly mutagenic in mammalian cells under standard test procedures, but can induce DNA damage, chromosomal aberrations, and micronuclei *in vitro* and *in vivo*. However, delayed mutagenecity and chromosomal instability are observed a long time after treatment of cells with nickel. Nickel compounds act as co-mutagens with a variety of DNA-damaging agents. Thus, disturbances of DNA repair appear to be important. A further important mechanism is the occurrence of epigenetic changes, mediated by altered DNA methylation patterns, and histone modification. Inflammation may also contribute to nickel-induced carcinogenesis.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of mixtures that include nickel compounds and nickel metal. These agents cause cancers of the lung and of the nasal cavity and paranasal sinuses.

There is *sufficient evidence* in experimental animals for the carcinogenicity of nickel monoxides, nickel hydroxides, nickel sulfides (including

nickel subsulfide), nickel acetate, and nickel metal.

There is *limited evidence* in experimental animals for the carcinogenicity of nickelocene, nickel carbonyl, nickel sulfate, nickel chloride, nickel arsenides, nickel antimonide, nickel selenides, nickel sulfarsenide, and nickel telluride.

There is *inadequate evidence* in experimental animals for the carcinogenicity of nickel titanate, nickel trioxide, and amorphous nickel sulfide.

In view of the overall findings in animals, there is *sufficient evidence* in experimental animals for the carcinogenicity of nickel compounds and nickel metal.

Nickel compounds are *carcinogenic to humans (Group 1).*

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ASBESTOS (CHRYSOTILE, AMOSITE, CROCIDOLITE, TREMOLITE, ACTINOLITE, AND ANTHOPHYLLITE)

Asbestos was considered by previous IARC Working Groups in 1972, 1976, and 1987 (IARC, 1973, 1977, 1987a). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Asbestos is the generic commercial designation for a group of naturally occurring mineral silicate fibres of the serpentine and amphibole series. These include the serpentine mineral chrysotile (also known as 'white asbestos'), and the five amphibole minerals – actinolite, amosite (also known as 'brown asbestos'), anthophyllite, crocidolite (also known as 'blue asbestos'), and tremolite (IARC, 1973; USGS, 2001). The conclusions reached in this *Monograph* about asbestos and its carcinogenic risks apply to these six types of fibres wherever they are found, and that includes talc containing asbestiform fibres. Erionite (fibrous aluminosilicate) is evaluated in a separate *Monograph* in this volume.

Common names, Chemical Abstracts Service (CAS) Registry numbers and idealized chemical formulae for the six fibrous silicates designated as 'asbestos' are presented in Table 1.1. Specific chemical and physical properties are also presented.

1.2 Chemical and physical properties of the agent

The silicate tetrahedron (SiO_4) is the basic chemical unit of all silicate minerals. The number of tetrahedra in the crystal structure and how they are arranged determine how a silicate mineral is classified.

Serpentine silicates are classified as 'sheet silicates' because the tetrahedra are arranged to form sheets. Amphibole silicates are classified as 'chain silicates' because the tetrahedra are arranged to form a double chain of two rows aligned side by side. Magnesium is coordinated with the oxygen atom in serpentine silicates. In amphibole silicates, cationic elements such as aluminium, calcium, iron, magnesium, potassium, and sodium are attached to the tetrahedra. Amphiboles are distinguished from one another by their chemical composition. The chemical formulas of asbestos minerals are idealized. In

Table 1.1 Common names, CAS numbers, synonyms, non-asbestos mineral analogues, idealized chemical formulae, selected physical and chemical properties of asbestos minerals

Common Name	CAS No.	Synonyms	Non-Asbestos Mineral Analogue	Idealized Chemical Formula	Colour	Decomposition Temperature (°C)	Other Properties
Asbestos	1332-21-4*	Unspecified		Unspecified			
Serpentine group of minerals							
Chrysotile	12001-29-5*	Serpentine asbestos; white asbestos	Lizardite, antigorite	$[Mg_3Si_2O_5(OH)_4]_n$	White, grey, green, yellowish	600–850	Curled sheet silicate, hollow central core; fibre bundle lengths = several mm to more than 10 cm; fibres more flexible than amphiboles; net positive surface charge; forms a stable suspension in water; fibres degrade in dilute acids
Amphibole group of minerals							
Crocidolite	12001-28-4*	Blue asbestos	Riebeckite	$[NaFe^{2+}_3Fe^{3+}_2Si_8O_{22}(OH)_2]_n$	Lavender, blue green	400–900	Double chain silicate; shorter, thinner fibres than other amphiboles, but not as thin as chrysotile; fibre flexibility: fair to good; spinnability: fair; resistance to acids: good; less heat resistance than other asbestos fibres; usually contains organic impurities, including low levels of PAHs; negative surface charge in water
Amosite	12172-73-5*	Brown asbestos	Grunerite	$[(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2]_n$	Brown, grey, greenish	600–900	Double chain silicate; long, straight, coarse fibres; fibre flexibility: somewhat; resistance to acids: somewhat; occurs with more iron than magnesium; negative surface charge in water
Anthophyllite	77536-66-4*	Ferroanthophyllite; azbolen asbestos	Anthophyllite	$[(Mg, Fe^{2+})_7Si_8O_{22}(OH)_2]_n$	Grey, white, brown-grey, green	NR	Double chain silicate; short, very brittle fibres; resistance to acids: very; relatively rare; occasionally occurs as contaminant in talc deposits; negative surface charge in water
Actinolite	77536-67-5*	Unspecified	Actinolite	$[Ca_2(Mg, Fe^{2+})_5Si_8O_{22}(OH)_2]_n$	Green	NR	Double chain silicate; brittle fibres; resistance to acids: none; occurs in asbestiform and non-asbestiform habit; iron-substituted derivative of tremolite; common contaminant in amosite deposits; negative surface charge in water
Tremolite	77536-68-6*	Silicic acid; calcium magnesium salt (8:4)	Tremolite	$[Ca_2Mg_5Si_8O_{22}(OH)_2]_n$	White to pale green	950–1040	Double chain silicate; brittle fibres; acid resistant; occurs in asbestiform and non-asbestiform habit; common contaminant in chrystotile and talc deposits; negative surface charge in water

* identified as asbestos by CAS Registry
NR, not reported
From ATSDR (2001), USGS (2001), HSE (2005), NTP (2005)

natural samples, the composition varies with respect to major and trace elements (USGS, 2001; HSE, 2005). More detailed information on the chemical and physical characteristics of asbestos – including atomic structure, crystal polytypes, fibre structure, chemistry and impurities – can be found in the previous *IARC Monograph* (IARC, 1973).

The structure of silicate minerals may be fibrous or non-fibrous. The terms 'asbestos' or 'asbestiform minerals' refer only to those silicate minerals that occur in polyfilamentous bundles, and that are composed of extremely flexible fibres with a relatively small diameter and a large length. These fibre bundles have splaying ends, and the fibres are easily separated from one another (USGS, 2001; HSE, 2005). Asbestos minerals with crystals that grow in two or three dimensions and that cleave into fragments, rather than breaking into fibrils, are classified as silicate minerals with a 'non-asbestiform' habit. These minerals may have the same chemical formula as the 'asbestiform' variety. (NIOSH, 2008).

Chrysotile, lizardite, and antigorite are the three principal serpentine silicate minerals. Of these, only chrysotile occurs in the asbestiform habit. Of the amphibole silicate minerals, amosite and crocidolite occur only in the asbestiform habit, while tremolite, actinolite and anthophyllite occur in both asbestiform and non-asbestiform habits (USGS, 2001; HSE, 2005; NTP, 2005).

Historically, there has been a lack of consistency in asbestos nomenclature. This frequently contributed to uncertainty in the specific identification of asbestos minerals reported in the literature. The International Mineralogical Association (IMA) unified the current mineralogical nomenclature under a single system in 1978. This system was subsequently modified in 1997 (NIOSH, 2008).

Asbestos fibres tend to possess good strength properties (e.g. high tensile strength, wear and friction characteristics); flexibility (e.g. the ability to be woven); excellent thermal properties (e.g. heat stability; thermal, electrical and acoustic insulation); adsorption capacity; and, resistance to chemical, thermal and biological degradation (USGS, 2001; NTP, 2005).

1.3 Use of the agent

Asbestos has been used intermittently in small amounts for thousands of years. Modern industrial use dates from about 1880, when the Quebec chrysotile fields began to be exploited. During the next 50 years gradual increases in production and use were reported with a cumulative total of somewhat less than 5000 million kg mined by 1930 (IARC, 1973).

As described above, asbestos has several chemical and physical properties that make it desirable for a wide range of industrial applications. By the time industrial and commercial use of asbestos peaked, more than 3000 applications or types of products were listed (NTP, 2005). Production and consumption of asbestos has declined in recent years due to the introduction of strict regulations governing exposure and/or outright bans on exposure.

Asbestos is used as a loose fibrous mixture, bonded with other materials (e.g. Portland cement, plastics and resins), or woven as a textile (ATSDR, 2001). The range of applications in which asbestos has been used includes: roofing, thermal and electrical insulation, cement pipe and sheets, flooring, gaskets, friction materials (e.g. brake pads and shoes), coating and compounds, plastics, textiles, paper, mastics, thread, fibre jointing, and millboard (USGS, 2001; NTP, 2005; Virta, 2006). Certain fibre characteristics, such as length and strength, are used to determine the most appropriate application. For example, longer fibres tend to be used in the production of textiles, electrical insulation, and filters; medium-length fibres are used in the production of asbestos cement pipes and sheets, friction materials (e.g. clutch facings, brake linings), gaskets, and pipe coverings; and,

short fibres are used to reinforce plastics, floor tiles, coatings and compounds, and roofing felts (NTP, 2005).

Since peaking in the 1970s, there has been a general decline in world production and consumption of asbestos. Peak world production was estimated to be 5.09 million metric tons in 1975, with approximately 25 countries producing asbestos and 85 countries manufacturing asbestos products (USGS, 2001; Nishikawa *et al.*, 2008). Worldwide 'apparent consumption' of asbestos (calculated as production plus imports minus exports) peaked at 4.73 million metric tons in 1980. Asbestos cement products are estimated to have accounted for 66% of world consumption in that year (Virta, 2006). In the USA, consumption of asbestos peaked in 1973 at 719000 metric tons (USGS, 2001).

Historical trends worldwide in per capita asbestos use are presented in Table 1.2, and peak use of asbestos was higher and occurred earlier in the countries of Northern and western Europe, Oceania, and the Americas (excluding South America). Very high asbestos use was recorded in Australia (5.1 kg per capita/year in the 1970s), Canada (4.4 kg per capita/year in the 1970s), and several countries of Northern and western Europe (Denmark: 4.8 kg per capita/year in the 1960s; Germany: 4.4 kg per capita/year in the 1970s; and Luxembourg: 5.5 kg per capita/year in the 1960s) (Nishikawa *et al.*, 2008).

Current use of asbestos varies widely. While some countries have imposed strict regulations to limit exposure and others have adopted bans, some have intervened less, and continue to use varying quantities of asbestos (Table 1.2). According to recent estimates by the US Geological Survey, world production of asbestos in 2007 was 2.20 million metric tonnes, slightly increased from 2.18 million metric ton in 2006. Six countries accounted for 96% of world production in 2006: the Russian Federation (925000 metric tons), the People's Republic of China (360000 metric tons), Kazakhstan (300000 metric tons), Brazil (227304 metric tons), Canada (185000 metric tons), and Zimbabwe (100000 metric tons) (Virta, 2008). During 2000–03, asbestos consumption increased in China, India, Kazakhstan, and the Ukraine (Virta, 2006). 'Apparent' world consumption of asbestos was 2.11 million metric tons in 2003, with the Russian Federation, several former Russian states and countries in Asia being the predominant users (Virta, 2006). Consumption of asbestos in the USA (predominantly chrysotile) was 2230 metric tons in 2006, declining to 1730 metric tons in 2007 (Virta, 2008). Roofing products (includes coatings and compounds) accounted for over 80% of asbestos consumption in the USA (Virta, 2008; Virta, 2009). Asbestos products were banned in all the countries of the European Union, including Member States of eastern Europe, effective January 1, 2005 (EU, 1999).

1.4 Environmental occurrence

1.4.1 Natural occurrence

Asbestos minerals are widespread in the environment, and are found in many areas where the original rock mass has undergone metamorphism (ATSDR, 2001; USGS, 2001). Examples include large chrysotile deposits in the Ural Mountains in the Russian Federation, in the Appalachian Mountains in the USA, and in Canada (Virta, 2006). They may occur in large natural deposits or as contaminants in other minerals (e.g. tremolite asbestos may occur in deposits of chrysotile, vermiculite, and talc). The most commonly occurring form of asbestos is chrysotile, and its fibres are found as veins in serpentine rock formations. Asbestiform amphiboles occur in relatively low quantities throughout the earth's crust and their chemical composition reflects the environment in which they form (Virta, 2002). Although most commercial deposits typically contain 5–6% of asbestos, a few deposits, such

Table 1.2 Historical trend in asbestos use per capita and status of national ban

	Use of asbestos[a] (kg per capita/year)						
Country	1950s	1960s	1970s	1980s	1990s	2000s	National ban[b]
Asia							
Israel	3.13	2.87	1.23	0.78	0.44	0.02	No ban
Japan	0.56	2.02	2.92	2.66	1.81	0.46	2004
Others[c] (n = 39)	0.06	0.15	0.25	0.27	0.30	0.31	3/39
Eastern Europe and Southern Europe							
Croatia	0.39	1.13	2.56	2.36	0.95	0.65	No ban
Czech Republic	1.62	2.36	2.91	2.73	1.30	0.14	2005
Hungary	0.76	1.23	2.87	3.29	1.50	0.16	2005
Poland	0.36	1.24	2.36	2.09	1.05	0.01	1997
Romania	ND	ND	1.08	0.19	0.52	0.55	2007
Spain	0.32	1.37	2.23	1.26	0.80	0.18	2002
Others[c] (n = 15)	0.79	1.57	2.35	2.05	2.35	1.72	5/15
Northern Europe and Western Europe							
Austria	1.16	3.19	3.92	2.08	0.36	0.00	1990
Denmark	3.07	4.80	4.42	1.62	0.09	NA	1986
Finland	2.16	2.26	1.89	0.78	ND	0	1992
France	1.38	2.41	2.64	1.53	0.73	0.00	1996
Germany	1.84	2.60	4.44	2.43	0.10	0.00	1993
Iceland	0.21	2.62	1.70	0.02	0	0.00	1983
Lithuania	ND	ND	ND	ND	0.54	0.06	2005
Luxembourg	4.02	5.54	5.30	3.23	1.61	0.00	2002
Netherlands	1.29	1.70	1.82	0.72	0.21	0.00	1994
Norway	1.38	2.00	1.16	0.03	0	0.00	1984
Sweden	1.85	2.30	1.44	0.11	0.04	NA	1986
United Kingdom	2.62	2.90	2.27	0.87	0.18	0.00	1999
Others[c] (n = 5)	3.05	4.32	4.05	2.40	0.93	0.05	5/5

as the Coalinga chrysotile deposits in California, USA, are reported to contain 50% or more (USGS, 2001; Virta, 2006).

1.4.2 Air

Asbestos is not volatile; however, fibres can be emitted to the atmosphere from both natural and anthropogenic sources. The weathering of asbestos-bearing rocks is the primary natural source of atmospheric asbestos. No estimates of the amounts of asbestos released to the air from natural sources are available (ATSDR, 2001). Anthropogenic activities are the predominant source of atmospheric asbestos fibres. Major anthropogenic sources include: open-pit mining operations (particularly drilling and blasting); crushing, screening, and milling of the ore; manufacturing asbestos products; use of asbestos-containing materials (such as clutches and brakes on cars and trucks); transport and disposal of wastes containing asbestos; and, demolition of buildings constructed with asbestos-containing products, such as insulation, fireproofing, ceiling and floor tiles, roof shingles, drywall, and cement (ATSDR, 2001; NTP, 2005). Concentrations of asbestos vary on a site-by-site basis and, as a result, environmental emissions are not easily estimated (ATSDR, 2001).

Table 1.2 (continued)

Country	Use of asbestos[a] (kg per capita/year)						
	1950s	1960s	1970s	1980s	1990s	2000s	National ban[b]
Americas, excluding South America							
Canada	2.76	3.46	4.37	2.74	1.96	0.32	No ban
Cuba	ND	ND	ND	0.15	0.36	0.74	No ban
Mexico	0.28	0.57	0.97	0.77	0.39	0.26	No ban
USA	3.82	3.32	2.40	0.77	0.08	0.01	No ban
Others[c] (n = 12)	0.06	0.22	0.44	0.29	0.07	0.07	0/12
South America							
Argentina	ND	0.88	0.76	0.40	0.18	0.04	2001
Brazil	0.27	0.38	0.99	1.25	1.07	0.74	2001
Chile	0.07	0.92	0.56	0.64	0.55	0.03	2001
Ecuador	ND	ND	0.67	0.52	0.14	0.26	No ban
Uruguay	ND	0.74	0.75	0.54	0.47	0.08	2002
Others[c] (n = 6)	0.27	0.43	0.60	0.47	0.29	0.19	0/6
Oceania							
Australia	3.24	4.84	5.11	1.82	0.09	0.03	2003
New Zealand	2.05	2.56	2.90	1.00	ND	ND	No ban
Others[c] (n = 3)	ND	ND	ND	ND	ND	0.22	0/3

[a] Numbers corresponding to use of asbestos by country and region were calculated as annual use per capita averaged over the respective decade.
[b] Year first achieved or year planned to achieve ban. When shown as fraction, the numerator is the number of countries that achieved bans and the denominator is the number of other countries in the region.
[c] Data on asbestos use were available (but mortality data unavailable) for others in each region, in which case data were aggregated.
ND, no data available; NA, not applicable because of negative use data; 0.00 when the calculated data were < 0.005; 0 if there are no data after the year the ban was introduced.
From Nishikawa et al. (2008)

1.4.3 Water

Asbestos can enter the aquatic environment from both natural and anthropogenic sources, and has been measured in both ground- and surface-water samples. Erosion of asbestos-bearing rock is the principal natural source. Anthropogenic sources include: erosion of waste piles containing asbestos, corrosion of asbestos-cement pipes, disintegration of asbestos-containing roofing materials, and, industrial wastewater run-off (ATSDR, 2001).

1.4.4 Soil

Asbestos can enter the soil and sediment through natural (e.g. weathering and erosion of asbestos-bearing rocks) and anthropogenic (e.g. disposal of asbestos-containing wastes in landfills) sources. The practice of disposing asbestos-containing materials in landfills was more common in the past, and is restricted in many countries by regulation or legislation (ATSDR, 2001).

1.4.5 Environmental releases

According to the US EPA Toxics Release Inventory, total releases of friable asbestos to the environment (includes air, water, and soil) in 1999 were 13.6 million pounds from 86 facilities that reported producing, processing, or using asbestos (ATSDR, 2001). In 2009, total releases of 8.9 million pounds of friable asbestos were reported by 38 facilities (US EPA, 2010).

1.5 Human exposure

Inhalation and ingestion are the primary routes of exposure to asbestos. Dermal contact is not considered a primary source, although it may lead to secondary exposure to fibres, via ingestion or inhalation. The degree of penetration in the lungs is determined by the fibre diameter, with thin fibres having the greatest potential for deep lung deposition (NTP, 2005).

1.5.1 Exposure of the general population

Inhalation of asbestos fibres from outdoor air, and to a lesser degree in indoor air, is the primary route of exposure for the non-smoking general population. Exposure may also occur via ingestion of drinking-water, which has been contaminated with asbestos through erosion of natural deposits, erosion of asbestos-containing waste sites, corrosion of asbestos-containing cement pipes, or filtering through asbestos-containing filters. Families of asbestos-workers may be exposed via contact with fibres carried home on hair or on clothing.

In studies of asbestos concentrations in outdoor air, chrysotile is the predominant fibre detected. Low levels of asbestos have been measured in outdoor air in rural locations (typical concentration, 10 fibres/m^3 [f/m^3]). Typical concentrations are about 10-fold higher in urban locations and about 1000 times higher in close proximity to industrial sources of exposure (e.g. asbestos mine or factory, demolition site, or improperly protected asbestos-containing waste site) (ATSDR, 2001). Asbestos fibres (mainly chrysotile) were measured in air and in settled dust samples obtained in New York City following destruction of the World Trade Center on September 11, 2001 (Landrigan *et al.*, 2004).

In indoor air (e.g. in homes, schools, and other buildings), measured concentrations of asbestos are in the range of 30–6000 f/m^3. Measured concentrations vary depending on the application in which the asbestos was used (e.g. insulation versus ceiling or floor tiles), and on the condition of the asbestos-containing materials (i.e. good condition versus deteriorated and easily friable) (ATSDR, 2001).

1.5.2 Occupational exposure

Asbestos has been in widespread commercial use for over 100 years (USGS, 2001). Globally, each year, an estimated 125 million people are occupationally exposed to asbestos (WHO, 2006). Exposure by inhalation, and to a lesser extent ingestion, occurs in the mining and milling of asbestos (or other minerals contaminated with asbestos), the manufacturing or use of products containing asbestos, construction, automotive industry, the asbestos-abatement industry (including the transport and disposal of asbestos-containing wastes).

Estimates of the number of workers potentially exposed to asbestos in the USA have been reported by the National Institute of Occupational Safety and Health (NIOSH), by the Occupational Safety and Health Administration (OSHA), and the Mine Safety and Health Administration (MSHA). OSHA estimated in 1990 that about 568000 workers in production and services industries and 114000 in construction industries may have been exposed to asbestos in the workplace (OSHA, 1990). Based on mine employment data from 2002, NIOSH estimated that 44000 miners and other mine workers may have been exposed to asbestos during the mining of asbestos and some mineral commodities in which asbestos may have been a potential contaminant (NIOSH, 2002b). More recently, OSHA has estimated that 1.3 million employees in construction and general industry face significant asbestos exposure on the job (OSHA, 2008). In addition to evidence from OSHA and MSHA that indicate a reduction in occupational exposures in the USA over the past several decades, other information compiled on workplace exposures to asbestos

indicates that the nature of occupational exposures to asbestos has changed (Rice & Heineman, 2003). Once dominated by chronic exposures in manufacturing process such as textile mills, friction-product manufacturing, and cement-pipe fabrication, current occupational exposures to asbestos primarily occur during maintenance activities or remediation of buildings that contain asbestos.

In Europe, estimates of the number of workers exposed to asbestos have been developed by CAREX (CARcinogen EXposure). Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX database estimates that a total of 1.2 million workers were exposed to asbestos in 41 industries in the 15 Member States of the EU. Over 96% of these workers were employed in the following 15 industries: 'construction' (n = 574000), 'personal and household services' (n = 99000), 'other mining' (n = 85000), 'agriculture' (n = 81000), 'wholesale and retail trade and restaurants and hotels' (n = 70000), 'food manufacturing' (n = 45000), 'land transport' (n = 39000), 'manufacture of industrial chemicals' (n = 33000), 'fishing' (n = 25000), 'electricity, gas and steam' (n = 23000), 'water transport' (n = 21000), 'manufacture of other chemical products' (n = 19000), 'manufacture of transport equipment' (n = 17000), 'sanitary and similar services' (n = 16000), and 'manufacture of machinery, except electrical' (n = 12000). Despite the total ban of asbestos, about 1500 workers (mainly construction workers and auto mechanics) were reported as having exposure to asbestos on the Finnish Register of Workers Exposed to Carcinogens (ASA Register) in 2006 (Saalo *et al.*, 2006). In 2004, approximately 61000 workers performing demolition and reconstruction work in Germany were registered in the Central Registration Agency for Employees Exposed to Asbestos Dust (Hagemeyer *et al.*, 2006).

Exposure to asbestos in occupational settings is regulated in countries of the EU. According to the European Directive of the EC 2003/18, permissible limits are 0.1 [f/mL] for all types of asbestos, based on an 8-hour time-weighted average (8h-TWA) (EU, 2003). The same limit is in force in most Canadian provinces (Alberta, British Columbia, Manitoba, Ontario, Newfoundland and Labrador, Prince Edward Island, New Brunswick and Nova Scotia); New Zealand; Norway; and, the USA. Other countries have permissible limits of up to 2 fibres/cm^3 (ACGIH, 2007).

Since 1986, the annual geometric means of occupational exposure concentrations to asbestos reported in the OSHA database and the MSHA database have been consistently below the NIOSH recommended exposure limit (REL) of 0.1 f/mL for all major industry divisions in the USA. The number of occupational asbestos exposure samples that were measured and reported by OSHA decreased from an average of 890 per year during 1987–94 to 241 per year during 1995–99. The percentage exceeding the NIOSH REL decreased from 6.3% during 1987–1994 to 0.9% during 1995–99. During the same two periods, the number of exposures measured and reported in the MSHA database decreased from an average of 47 per year during 1987–94 to an average of 23 per year during 1995–99. The percentage exceeding the NIOSH REL decreased from 11.1% during 1987–94 to 2.6% during 1995–99 (NIOSH, 2002a).

Data from studies and reviews of occupational asbestos exposure published since the previous *IARC Monograph* (IARC, 1973) are summarized below.

(a) Studies of occupational exposure

In a mortality study of 328 employees of an asbestos-cement factory in Ontario, Canada, Finkelstein (1983) constructed an exposure model on the basis of available air sampling data, and calculated individual exposure histories to

investigate exposure–response relationships for asbestos-associated malignancies. In retrospectively estimating exposure, the following assumptions were made: exposures did not change during 1962–70, exposures during 1955–61 were 30% higher than the later period, and exposures during 1948–54 were twice as high as during 1962–70. Exposure estimates for the years 1949, 1969, and 1979 were as follows: 40, 20, 0.2 f/mL for the willows operators; 16, 8, 0.5 f/mL for the forming machine operators; and, 8, 4, 0.3 f/mL for the lathe operators.

In an occupational hygiene survey of 24 Finnish workplaces, asbestos concentrations were measured during the different operations of brake maintenance of passenger cars, trucks and buses. During brake repair of trucks or buses, the estimated 8-hour time-weighted average exposure to asbestos was 0.1–0.2 [f/mL]. High levels of exposure (range, 0.3–125 [f/mL]; mean, 56 [f/mL]) were observed during brake maintenance if local exhaust ventilation was not used. Other operations in which the concentration exceeded 1 [f/mL] included cleaning of brakes with a brush, wet cloth or compressed air jet without local exhaust (Kauppinen & Korhonen, 1987).

Kimura (1987), in Japan, reported the following geometric mean concentrations: bag opening and mixing, 4.5–9.5 f/mL in 1970–75 and 0.03–1.6 f/mL in 1984–86; cement cutting and grinding, 2.5–3.5 f/mL in 1970–75 and 0.17–0.57 f/mL in 1984–86; spinning and grinding of friction products, 10.2–35.5 f/mL in 1970–75 and 0.24–5.5 f/mL in 1984–86.

Albin *et al.* (1990) examined total and cause-specific mortality among 1929 Swedish asbestos cement workers employed at a plant producing various products (e.g. sheets, shingles, ventilation pipes) from chrysotile and, to a lesser extent, crocidolite and amosite asbestos. Individual exposures were estimated using dust measurements available for the period 1956–77. Levels of exposure were estimated for the following operations: milling, mixing, machine line, sawing, and grinding. Asbestos concentrations ranged from 1.5–6.3 f/mL in 1956, to 0.3–5.0 f/mL in 1969, and to 0.9–1.7 f/mL in 1975. In all three time periods, the highest concentrations were observed in the milling and grinding operations.

The Health Effects Institute (1991) evaluated an operation and maintenance programme in a hospital on the basis of 394 air samples obtained during 106 on-site activities. The mean asbestos concentration was approximately 0.11 f/mL for personal samples, and approximately 0.012 f/mL for area samples. Eight-hour TWA concentrations showed that 99% of the personal samples were below 0.2 f/mL, and 95% below 0.1 f/mL.

Price *et al.* (1992) estimated the TWAs of asbestos exposures experienced by maintenance personnel on the basis of 1227 air samples collected to measure airborne asbestos levels in buildings with asbestos-containing materials. TWA exposures were 0.009 f/mL for telecommunication switch work, 0.037 f/mL for above-ceiling maintenance work, and 0.51 f/mL for work in utility spaces. Median concentrations were in the range of 0.01–0.02 f/mL.

Weiner *et al.* (1994) reported concentrations in a South African workshop in which chrysotile asbestos cement sheets were cut into components for insulation. The sheets were cut manually, sanded and subsequently assembled. Initial sampling showed personal sample mean concentrations of 1.9 f/mL for assembling, 5.7 f/mL for sweeping, 8.6 f/mL for drilling, and 27.5 f/mL for sanding. After improvements and clean-up of the work environment, the concentrations fell to 0.5–1.7 f/mL.

In a 1985 study, Higashi *et al.* (1994) collected personal and area samples at two manufacturing and processing locations in five Japanese plants manufacturing asbestos-containing products (a roofing material plant; a plant making asbestos cement sheets; a friction-material plant; and two construction and roofing-material plants). Geometric average concentrations of 0.05–0.45

f/mL were measured in area samples, and 0.05–0.78 f/mL in personal samples.

To assess the contribution of occupational asbestos exposure to the occurrence of mesothelioma and lung cancer in Europe, Albin *et al.* (1999) reviewed and summarized the available information on asbestos consumption in Europe, the proportion of the population exposed and levels of exposure. Ranges of exposure were reported for the former Yugoslavia, Poland, and Latvia. In 1987, mean fibre concentrations in Serbia and Montenegro were 2–16 f/mL for textile manufacturing, 3–4 f/mL for friction materials production, and 1–4 f/mL for asbestos cement production. In Poland, exposure levels in 1994 were estimated to be much greater than 2 f/mL in the textile industry, approximately 2 f/mL in asbestos cement and friction-products manufacturing, and greater than 0.5 f/mL in downstream use. In the Latvian asbestos cement industry in 1994, ranges of fibre concentrations were 0.1–1.1 f/mL for the machine line, and 1.1–5.2 f/mL for the milling and mixing areas.

Since 1974, NIOSH has conducted a series of sampling surveys in the USA to gather information on exposure of brake mechanics to airborne asbestos during brake repair. These surveys indicated that the TWA asbestos concentrations (about 1–6 hours in duration) during brake servicing were in the range of 0.004–0.28 f/mL, and the mean TWA concentration, approxiamtely 0.05 f/mL (Paustenbach *et al.*, 2004).

Based on a review of the historical literature on asbestos exposure before 1972 and an analysis of more than 26000 measurements collected during 1972–90, Hagemeyer *et al.* (2006) observed a continual decrease in workplace levels of airborne asbestos from the 1950s to 1990 in Western Germany (FRG) and Eastern Germany (GDR). High concentrations of asbestos fibres were measured for some working processes in Western Germany (e.g. asbestos spraying (400 [f/mL]), removal of asbestos insulations in the ship repair industry (320 [f/mL]), removal of asbestos insulation (300 [f/mL]), and cutting corrugated asbestos sheets (60 [f/mL]), see Table 1.3.

In a study at a large petroleum refinery in Texas, USA, Williams *et al.* (2007a) estimated 8h-TWA asbestos exposures for 12 different occupations (insulators, pipefitters, boilermakers, masons, welders, sheet-metal workers, millwrights, electricians, carpenters, painters, laborers, and maintenance workers) from the 1940s to the 1985 onwards. Estimates were calculated using information on the historical use of asbestos, the potential for exposure due to daily work activities, occupational hygiene sampling data, historical information on task-specific exposures, and use of personal protective equipment. Exposures were estimated for 1940–50, 1951–65, 1966–71, 1972–75, 1976–85, and 1985 onwards. For these time periods, the 8h-TWA exposure (50^{th} percentile) estimates for insulators were, respectively, 9 f/mL, 8 f/mL, 2 f/mL, 0.3 f/mL, 0.005 f/mL, and < 0.001 f/mL. For all other occupations, with the exception of labourers, estimated 8h-TWA exposure estimates were at least 50- to 100-fold less than that of insulators. Estimated 8h-TWA exposure estimates for labourers were approximately one-fifth to one-tenth of those of insulators.

Williams *et al.* (2007b) reviewed historical asbestos exposures (1940–2006) in various non-shipyard and shipyard settings for the following skilled occupations: insulators, pipefitters, boilermakers, masons, welders, sheet-metal workers, millwrights, electricians, carpenters, painters, labourers, maintenance workers, and abatement workers. For activities performed by insulators in various non-shipyard settings from the late 1960s and early 1970s, average task-specific and/or full-shift airborne fibre concentrations ranged from about 2 to 10 f/mL. Average fibre concentrations in US shipyards were about 2-fold greater, and excessively high concentrations (attributed to the spraying of asbestos) were reported in some British Naval shipyards. The introduction of improved occupational hygiene

Table 1.3 Examples of asbestos fibre concentrations in the air (f/cm³) of different workplaces in Germany

Work area		1950–54[a]	1970–74	1980	1990
Textile industries	FRG	100	10	3.8	0.9
	GDR	100	12	6.2	2.2
Production of gaskets	FRG	60	6.6	4.7	0.7
	GDR	60	8.0	7.8	1.6
Production of cement	FRG	200	11	1.1	0.3
	GDR	200	13	1.9	0.7
Production of brake pads	FRG	150	9.1	1.4	0.7
	GDR	150	11	2.4	1.6
Insulation works	FRG	15	15	8.6	0.2
	GDR	18	18	14.0	0.5

[a] Data for the GDR before 1967 are extrapolated
FRG, Federal Republic of Germany; GDR, German Democratic Republic
From Hagemeyer et al. (2006)

practices resulted in a 2- to 5-fold reduction in average fibre concentrations for insulator tasks. The typical range of average fibre concentration for most other occupations was < 0.01–1 f/mL. Concentrations varied with task and time period, with higher concentrations observed for tasks involving the use of powered tools, the mixing or sanding of drywall cement, and the cleanup of asbestos insulation or lagging materials. It was not possible with the available data to determine whether the airborne fibres were serpentine or amphibole asbestos.

Madl *et al.* (2007) examined seven simulation studies and four work-site industrial hygiene studies to estimate the concentration of asbestos fibres to which workers may have historically been exposed while working with asbestos-containing gaskets and packing materials in specific industrial and maritime settings (e.g. refinery, chemical, ship/shipyard). These studies involved the collection of more than 300 air samples and evaluated specific activities, such as the removal and installation of gaskets and packings, flange cleaning, and gasket formation. In all but one of the studies, the short-term average exposures were less than 1 f/mL, and all of the long-term average exposures were less than 0.1 f/mL. Higher short-term average concentrations were observed during the use of powered tools versus hand-held manual tools during gasket formation (0.44 f/mL versus 0.1 f/mL, respectively). Peak concentrations of 0.14 f/mL and 0.40 f/mL were observed during 'gasket removal and flange face cleaning with hand tools' and 'packing removal and installation', respectively.

(b) Dietary exposure

The general population can be exposed to asbestos in drinking-water. Asbestos can enter potable water supplies through the erosion of natural deposits or the leaching from waste asbestos in landfills, from the deterioration of asbestos-containing cement pipes used to carry drinking-water or from the filtering of water supplies through asbestos-containing filters. In the USA, the concentration of asbestos in most drinking-water supplies is less than 1 f/mL, even in areas with asbestos deposits or with asbestos cement water supply pipes. However, in some locations, the concentration in water may be extremely high, containing 10–300 million f/L (or even higher). The average person drinks about 2 litres of water per day (ATSDR, 2001). Risks of exposure to asbestos in drinking-water

may be especially high for small children who drink seven times more water per day per kg of body weight than the average adult (National Academy of Sciences, 1993).

1.6 Talc containing asbestiform fibres

Talc particles are normally plate-like. These particles, when viewed on edge under the microscope in bulk samples or on air filters, may appear to be fibres, and have been misidentified as such. Talc may also form true mineral fibres that are asbestiform in habit. In some talc deposits, tremolite, anthophyllite, and actinolite may occur. Talc containing asbestiform fibres is a term that has been used inconsistently in the literature. In some contexts, it applies to talc containing asbestiform fibres of talc or talc intergrown on a nanoscale with other minerals, usually anthophyllite. In other contexts, the term asbestiform talc has erroneously been used for talc products that contain asbestos. Similarly, the term asbestiform talc has erroneously been used for talc products that contain elongated mineral fragments that are not asbestiform. These differences in the use of the same term must be considered when evaluating the literature on talc. For a more detailed evaluation of talc not containing asbestiform fibres, refer to the previous *IARC Monograph* (IARC, 2010).

1.6.1 Identification of the agent

Talc (CAS No. 14807-96-6) is a designation for both the mineral talc and for commercial products marketed as 'talc', which contain the mineral in proportions in the range of 35% to almost 100%. Commercial talc is classified as 'industrial talc' (refers to products containing minerals other than talc), 'cosmetic talc' (refers to products, such as talcum powder, which contain > 98% talc), and 'pharmaceutical talc' (refers to products containing > 99% talc) (Rohl *et al.*, 1976; Zazenski *et al.*, 1995). Synonyms for talc include: Agalite, French chalk, kerolite, snowgoose, soapstone, steatite, talcite, and talcum.

1.6.2 Chemical and physical properties of the agent

The molecular formula of talc is $Mg_3Si_4O_{10}(OH)_2$. It is a hydrated magnesium sheet silicate mineral, whose structure is composed of a layer of $MgO_4(OH)_2$ octahedra sandwiched between identical layers of SiO_4 tetrahedra. In nature, the composition of talc varies depending on whether or not the magnesium has been substituted with other cations, such as iron, nickel, chromium or manganese (Rohl *et al.*, 1976; IMA, 2005). Pure talc is translucent, appearing white when finely ground (Zazenski *et al.*, 1995). The colour of talc changes in the presence of substituted cations, ranging from pale-green to dark-green, brownish or greenish-grey. Talc has the following chemical and physical properties: melting point, 1500°C; hardness, 1 on the Moh's scale of mineral hardness; density, 2.58–2.83; and cleavage, (001) perfect (Roberts *et al.*, 1974). Talc is a very stable mineral, and is insoluble in water, weak acids and alkalis, is neither explosive nor flammable, and has very little chemical reactivity (IMA, 2005).

Talc's structure is crystalline. It can have a small, irregular plate structure (referred to as microcrystalline talc) or it can have large, well defined platelets (referred to as macrocrystalline talc). Its platyness and crystallinity determine the specific commercial applications for which it is suitable (Zazenski *et al.*, 1995). Talc is formed by complex geological processes acting on pre-existing rock formations with diverse chemical composition (Rohl *et al.*, 1976). Many talc-bearing rocks are formed from magnesia- and silica-rich ultramafic rocks. These rocks have a central core of serpentinite surrounded by successive shells of talc-abundant rock (e.g. talc carbonate and steatite). The serpentinite core is composed mostly of non-asbestiform serpentine minerals (lizardite

and antigorite); however, small amounts of chrysotile asbestos may occur. (Zazenski *et al.*, 1995).

More detail on the chemical and physical properties of talc can be found in the previous *IARC Monograph* (IARC, 2010).

1.6.3 Use of the agent

Talc has several unique chemical and physical properties (such as platyness, softness, hydrophobicity, organophilicity, inertness) that make it desirable for a wide range of industrial and commercial applications (e.g. paint, polymers, paper, ceramics, animal feed, rubber, roofing, fertilizers, and cosmetics). In these products, talc acts as an anti-sticking and anti-caking agent, lubricant, carrier, thickener, absorbent, and strengthening and smoothing filler (IMA, 2005).

In 2000, the worldwide use pattern for talc was as follows: paper industry, 30%; ceramics manufacture, 28%; refractories, 11%; plastics, 6%; filler or pigment in paints, 5%; roofing applications, 5%; cement, 3%; cosmetics, 2%; and other miscellaneous uses, 10% (includes agriculture and food, art sculpture, asphalt filler, autobody filler, construction caulks, flooring, and joint compounds) (Roskill Information Services Ltd, 2003). According to a Mineral Commodity Summary published by the USGS in 2009, talc produced in the USA was used for ceramics, 31%; paper, 21%; paint, 19%; roofing, 8%; plastics, 5%; rubber, 4%; cosmetics, 2%; and other, 10% (Virta, 2009).

No information on the use of asbestiform talc in various industries (apart from mining and milling of talc from deposits containing asbestiform fibres) was identified by the Working Group. For a more detailed description of the uses of talc, refer to the previous *IARC Monograph* (IARC, 2010).

1.6.4 Environmental occurrence

(a) Natural occurrence

Primary talc deposits are found in almost every continent around the world. Talc is commonly formed by the hydrothermal alteration of magnesium- and iron-rich rocks (ultramafic rocks) and by low-grade thermal metamorphism of siliceous dolomites (Zazenski *et al.*, 1995). For more detailed information on the formation of commercially important talc deposits, refer to the previous *IARC Monograph* (IARC, 2010).

Talc deposits whose protoliths are ultramafic rocks (or mafic) are abundant in number but small in total production. They are found in discontinuous bodies in orogenic belts such as the Alps, the Appalachians, and the Himalayas; these types of talc deposits form during regional metamorphism accompanying orogenesis. They also occur in the USA (California, Arkansas, Texas), Germany, Norway, Canada (Ontario and Quebec), southern Spain, Finland, the Russian Federation (Shabry and Miassy), and Egypt. Chlorite and amphibole are usually associated with this type of talc deposit although they are commonly separated in space from the talc ore (Vermont). The amphiboles may or may not be asbestiform, depending on the local geological history (IARC, 2010).

Talc deposits formed from the alteration of magnesian carbonate and sandy carbonate such as dolomite and limestone are the most important in terms of world production. Two types are recognized:

- those derived from hydrothermal alteration of unmetamorphosed or minimally metamorphosed dolomite such as found in Australia (Mount Seabrook and Three Springs); USA (Wintersboro, Alabama; Yellowstone, Montana; Talc City, California; Metaline Falls, Washington; and West Texas); the Republic of Korea; the People's Republic of China; India; the

Russian Federation (Onot); and, northern Spain (Respina)
- those derived from hydrothermal alteration (including retrograde metamorphism) of regionally metamorphosed siliceous dolomites and other magnesium-rich rocks such as in the USA (Murphy Marble belt, North Carolina; Death Valley-Kingston Range, California; Gouverneur District, New York; Chatsworth, Georgia); Canada (Madoc); Italy (Chisone Valley); the Russian Federation (Krasnoyarsk); Germany (Wunsiedel); Austria (Leoben); Slovakia (Gemerska); Spain; France (Trimouns); and Brazil (Brumado) (IARC, 2010).

In a study to examine the amphibole asbestos content of commercial talc deposits in the USA, Van Gosen *et al.* (2004) found that the talc-forming environment (e.g. regional metamorphism, contact metamorphism, or hydrothermal processes) directly influenced the amphibole and amphibole-asbestos content of the talc deposit. Specifically, the study found that hydrothermal talcs consistently lack amphiboles as accessory minerals, but that contact metamorphic talcs show a strong tendency to contain amphiboles, and regional metamorphic talc bodies consistently contain amphiboles, which display a variety of compositions and habits (including asbestiform). Death Valley, California is an example of a contact metamorphic talc deposit that contains accessory amphibole-asbestos (namely talc-tremolite).

1.6.5 Human exposure

(a) Exposure of the general population

Consumer products (e.g. cosmetics, pharmaceuticals) are the primary sources of exposure to talc for the general population. Inhalation and dermal contact (i.e. through perineal application of talcum powders) are the primary routes of exposure. As talc is used as an anti-sticking agent in several food preparations (e.g. chewing gum), ingestion may also be a potential, albeit minor, route of exposure.

As late as 1973, some talc products sold in the USA contained detectable levels of chrysotile asbestos, tremolite, or anthophyllite (Rohl *et al.*, 1976), and it is possible that they remained on the market in some places in the world for some time after that (Jehan, 1984). Some of the tremolite and anthophyllite may have been asbestiform in habit (Van Gosen, 2006).

Blount (1991) examined pharmaceutical- and cosmetic-grade talcs for asbestiform amphibole content using a density-optical method. High-grade talc product samples (n = 15) were collected from deposits in Montana, Vermont, North Carolina, Alabama, and from outside the USA but available in the US market. Samples were uniformly low in amphibole content (with counts in the range of 0–341 particles/mg), and some samples appeared to be completely free of amphibole minerals. In samples containing amphibole minerals, cleavage-type and asbestos-type minerals were observed. Only one sample was found to contain an amphibole particle size distribution typical of asbestos.

More complete information on the levels of exposure experienced by the general population can be found in the previous *IARC Monograph* (IARC, 2010).

(b) Occupational exposure

Inhalation is the primary route of exposure to talc in occupational settings. Exposure by inhalation to talc dust occurs in the talc-producing industries (e.g. during mining, crushing, separating, bagging, and loading), and in the talc-using industries (e.g. rubber dusting and addition of talcs to ceramic clays and glazes). Because industrial talc is a mixture of various associated minerals, occupational exposure is to a mixture of mineral dusts (IARC, 1987b).

In general, data on numbers of workers occupationally exposed to talc are lacking. The

National Occupation Exposure Survey (NOES), which was conducted by the US National Institute for Occupational Safety and Health (NIOSH) during 1981–83, estimated that 1.4 million workers, including approximately 350000 female workers, were potentially exposed to talc in the workplace (NIOSH, 1990). CAREX reports that approximately 28000 workers were exposed to talc containing asbestiform fibres in the workplace within the 15 countries that comprised the EU during 1990–93; however, some major industries producing or using talc were not included.

Many of the early measurements reported very high levels of talc dust exposures in mining and milling operations, often in the range of several mg/m^3, but there is evidence of decreasing exposures (IARC, 1987b; IARC, 2010). For example, before the adoption of technical preventive means in 1950, exposures in the talc operation in the Germanasca and Chisone Valley (Piedmont), Italy, were reported to be approximately 800 mppcf in the mines, and approximately 25 mppcf in the mills. Exposures in both areas were reduced to less than 10 mppcf after 1965 when improved occupational hygiene practices were implemented (Rubino *et al.*, 1976). Although the presence of asbestiform talc was often not reliably verified, it is likely that these levels have also decreased, in part due to mine closures and regulatory controls.

Oestenstad *et al.* (2002) developed a job–exposure matrix for respirable dust, covering all work areas in an industrial grade (tremolitic) talc mining and milling facility in upstate New York, USA. The facility started operating in 1948 with the opening of an underground mine (Mine 1) and a mill (Mill 1). An open pit mine (Mine 2) opened in 1974. Talc from the facility was used predominantly for manufacturing paint and ceramic tiles. The range of all respirable dust concentrations measured in the two baseline exposure surveys was 0.01–2.67 mg/m^3, with an arithmetic mean of 0.47 mg/m^3 and a geometric mean of 0.28 mg/m^3.

Only limited information is available about exposures in secondary industries in which talc is used or processed further. The previous *IARC Monograph* on talc (IARC, 2010) summarizes three historical surveys conducted in these kinds of industries. The IARC Working Group in 1987 noted, however, that even when measurements of respirable fibres were reported, no electron microscopic analysis was conducted to confirm the identity of the fibres. Recently, most industries using talc use non-asbestiform talc (IARC, 2010).

For a more complete description of studies in which occupational exposure to talc and talc-containing products has been reported, refer to the previous *IARC Monograph* (IARC, 2010).

2. Cancer in Humans

2.1 Introduction

The previous *IARC Monographs* were limited to the same six commercial forms of asbestos fibres (chrysotile, actinolite, amosite, anthophyllite crocidolite and tremolite) that are subject of this current evaluation. In the previous *IARC Monograph* (IARC, 1977), the epidemiological evidence showed a high incidence of lung cancer among workers exposed to chrysotile, amosite, anthophyllite, and with mixed fibres containing crocidolite, and tremolite. Pleural and peritoneal mesotheliomas were reported to be associated with occupational exposures to crocidolite, amosite, and chrysotile. Gastrointestinal tract cancers were reported to have been demonstrated in groups occupationally exposed to amosite, chrysotile or mixed fibres containing chrysotile. An excess of cancer of the larynx in occupationally exposed individuals was also noted. Finally the *Monograph* points out that mesothelioma may occur among individuals living in neighbourhoods of asbestos factories

and crocidolite mines, and in persons living with asbestos workers.

Extensive epidemiological research on asbestos has been conducted since then. The associations between asbestos exposure, lung cancer, and mesothelioma have been well established in numerous epidemiological investigations. The epidemiological evidence for other cancer sites is less extensive than it is for lung cancer and mesothelioma, but is still considerable for some. In reviewing these studies, there are some common limitations that need to be borne in mind, which may explain the heterogeneity of the findings from the studies such as:

- The types, fibre sizes and levels of asbestos exposure differed from industry to industry and over time. Most of the heaviest exposures probably occurred in the first two-thirds of the twentieth century in asbestos mining and milling, insulation work, shipyard work, construction, and asbestos textile manufacture. Workers in different industries, eras, and geographic locales were exposed to different types of asbestos fibres, and to fibres of greatly varying dimensions.
- There were differences in how the studies handle the issue of latency or in other words time since first occupational exposure to asbestos. Some studies, especially earlier investigations, accumulated person–years from first exposure, a procedure that may dilute observed risk by including many years of low risk. Others have only accumulated person–years after a certain period of time after first exposure, usually 20 years. Also different studies followed their populations for very different periods of time since first occupational exposure to asbestos.
- The most pervasive problem in interpreting studies was the wide variation among studies in the approaches taken for exposure assessment. Some studies made no attempt to assess exposure beyond documenting employment of study participants in a trade or industry with potential for occupational exposure to asbestos. Other studies used surrogate indices of exposure such as duration of employment or self-reported intensity of exposure, or stratified subjects' exposure by job title. Some used the skills and knowledge of industrial hygienists, obtained direct measurements of asbestos dust levels in air, and developed job–exposure matrices and cumulative exposure indices. Even these analyses are limited by the fact that earlier studies used gravimetric measures of dust exposure, while later used fibre-counting methods based on phase contrast microscopy (PCM). Factors that were used to convert between gravimetric and PCM based measurements are generally unreliable unless they are based on side by side measurements taken in specific industrial operations. Differences in fibre size distributions and fibre type can only be detected using electron microscopy, which has been done in only a very few studies.
- Misclassification of disease was a serious problem for several of the cancer sites. This is particularly true for mesothelioma, which did not have diagnostic category in the ICD system until the 10th review was initiated in 1999.

There were also issues regarding the potential for misclassification of mesotheliomas as colon or ovarian cancers.

For talc that contains asbestiform fibres, previous Working Groups assessed studies on talc described as containing asbestiform tremolite and anthophyllite (IARC, 1987a, b). These fibres fit the definition of asbestos, and therefore a separate review of talc containing asbestiform fibres was not undertaken by this Working Group. The reader is invited to consult the General Remarks

in this volume for further details. For a review of Talc, refer to the previous *IARC Monograph* (IARC, 2010).

2.2 Cancer of the lung

2.2.1 Occupational exposure

Signs that cancer of the lung could be induced by exposure to asbestos was first raised by reports of lung cancer cases that occurred among workers with asbestosis (Gloyne, 1935; Lynch & Smith, 1935). The first cohort study that demonstrated an excess of lung cancer among asbestos exposed workers was a study of textile workers (Doll, 1955). In this study, 11 cases of lung cancer versus 0.8 expected ($P < 0.00001$) were reported based on national mortality rates. Since 1955, an association between lung cancer and occupational exposure to asbestos has been demonstrated in numerous cohort and case–control studies that are summarized in Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.1.pdf, Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.2.pdf, and Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.3.pdf.

Although a causal association between asbestos exposure and lung cancer is generally well recognized, there are still substantial controversies on how the risk might vary by exposure to different fibre types and sizes, and whether there is a risk at low levels of exposure (i.e. environmental exposures). Particularly controversial is the question of whether chrysotile asbestos is less potent for the induction of lung cancer than the amphibole forms of asbestos (e.g. crocidolite, amosite and tremolite), which has sometimes been referred to as the "amphibole hypothesis" (Cullen, 1996; Stayner *et al.*, 1996; McDonald, 1998). This argument is based on the observation from experimental studies that chrysotile asbestos is less biopersistent (i.e. has a shorter half life) in the lung than the amphiboles. Pathological studies of tissue using electron microscopy and energy dispersive analysis of X-rays (EDAX) have been used to measure the amounts of different asbestos fibre types in the lung. Case studies of Canadian chrysotile asbestos workers using these methods have shown an unexpectedly high proportion of amphibole (primarily tremolite) fibres, considering the relatively low percentage of amphibole fibres in commercial chrysotile asbestos (Pooley, 1976; Rowlands *et al.*, 1982; Addison & Davies, 1990). [The Working Group noted that the lower biopersistence of chrysotile in the lung does not necessarily imply that it would be less potent than amphiboles for lung cancer.]

Several meta-analyses have been conducted in which the relative potency of different fibre types and other fibre characteristics have been considered in relation to lung cancer. Lash *et al.* (1997) conducted a meta-analysis based on the findings from 15 cohort studies with quantitative information on the relationship between asbestos exposure and lung cancer risk. The slopes of the lung cancer exposure–response relationship from these studies were analysed using fixed and random effects models. Substantial heterogeneity in the slopes for lung cancer from these studies was found in their analysis. The heterogeneity was largely explained by industry category, dose measurements, tobacco habits, and standardization procedures. There was no evidence in this meta-analysis that differences in fibre type explained the heterogeneity of the slope.

Hodgson & Darnton (2000) performed a meta-analysis based on 17 cohort studies with information on the average level of asbestos exposure for the cohort as a whole or for subgroups in the study. The percentage excess lung cancer risk from each study or subgroup was divided by its average exposure level to derive a slope (RL) for the analysis. Substantial heterogeneity in the findings for lung cancer was also found in this

analysis particularly for the chrysotile cohorts. The heterogeneity in the findings for the chrysotile cohorts was largely attributable to differences in the findings from the studies of chrysotile miners and millers in Quebec (McDonald *et al.*, 1983), and asbestos textile workers in South Carolina (Dement & Brown, 1994; Hein *et al.*, 2007), which differed by nearly 100-fold. No explanation has been found for these extreme differences although several possible explanations have been investigated. Co-exposure to mineral oils in the South Carolina textile plant was proposed as a possible explanation. A nested case–control conducted with the South Carolina cohort failed to provide evidence to support the hypothesis that mineral exposure was associated with an increased risk of lung cancer in this study population (Dement & Brown, 1994). Differences in fibre size distributions have also been considered to be a potential explanation. The asbestos textile industry workers may have used a higher grade of asbestos resulting in exposures to a greater percentage of long fibres than what was experienced by miners and millers in Quebec. A larger percentage of long fibres was found in a recent reanalysis of samples from the South Carolina cohort using transmission electron microscopy (TEM) (Dement *et al.*, 2008) than what was previously reported in TEM analyses of samples from the Quebec mines and mills (Gibbs & Hwang, 1975, 1980). Based on their analysis, Hodgson & Darnton (2000) concluded that the ratio between lung cancer risk for chrysotile and the amphiboles was somewhere between 1:10 and 1:50. However, in their analyses (where they excluded the study of Quebec miners rather than the South Carolina cohort), there was only a 2-fold difference in findings for lung cancer risk between the chrysotile (RL = 2.3) and amphibole cohorts (RL = 4.2). [The Working Group noted that there is no justification for exclusion of the South Carolina cohort because it is one of the highest quality studies in terms of the exposure information used in this study.]

Berman & Crump (2008a) published a meta-analysis that included data from 15 asbestos cohort studies. Lung cancer risk potency factors (Kis = [RR-1]/cumulative exposure) were derived in their analyses that were specific for both fibre type (chrysotile versus amphiboles) and fibre size (length and width). Fibre size information was only available for one of the cohort studies, and for the other studies it was obtained from studies that were conducted in similar industrial settings. As with the previous analyses, substantial variation was found in the findings from these studies with results for lung cancer varying by two orders of magnitude, although no formal statistical tests of heterogeneity were performed. The hypothesis that chrysotile is equipotent as the amphiboles for lung cancer was not rejected for fibres of all widths ($P = 0.07$) or for thick (width > 0.2 μm) fibres ($P = 0.16$). For thin fibres (width < 0.2 μm), there was significant ($P = 0.002$) evidence that chrysotile fibres were less potent than amphiboles. Sensitivity analyses were also conducted in which the South Carolina or Quebec miners and millers cohorts were dropped from the analysis using fibres of all widths. Dropping the South Carolina cohort resulted in a highly significant ($P = 0.005$) result that potency was greater for amphiboles than for chrysotile. Dropping the Quebec cohort resulted in there being no significant ($P = 0.55$) evidence of a difference in potency between the fibre types. [The Working Group noted that both the Hodgson & Darnton and Berman & Crump analyses reveal a large degree of heterogeneity in the study findings for lung cancer, and that findings are highly sensitive to the inclusion or exclusion of the studies from South Carolina or Quebec. The reasons for the heterogeneity are unknown, and until they are explained it is not possible to draw any firm conclusions concerning the relative potency of chrysotile and amphibole asbestos fibres from these analyses.]

Based on findings from experimental studies, it is suspected that long and thin fibres are likely

to be more potent than short and thick fibres in the induction of lung cancer in humans. Unfortunately until recently, all of the epidemiological studies that have been conducted used methods for exposure assessment that did not include a determination of fibre size, and thus this issue could not be directly addressed with these studies. As described above, the meta-analysis conducted by Berman & Crump (2008a) considered the effect of fibre size on lung cancer risk by using data from other studies conducted in similar circumstances as the cohort studies. Their analysis did not reveal strong evidence that lung cancer potency was dependent on fibre size. There was weak evidence that long fibres (length > 10 μm) were more potent than short fibres (5 μm < length < 10 μm) in models using all widths ($P = 0.07$). The lack of size-specific data from the studies was a major limitation of this study with regard to estimating size-specific risk estimates. Stayner *et al.* (2008) published findings from an analysis of the South Carolina asbestos textile cohort in which fibre size specific estimates of lung cancer mortality was evaluated using information from a reanalysis of archived air samples using TEM (Dement *et al.*, 2008). Long fibres (> 10 μm) and thin fibres (< 0.25 μm) were found to be the strongest predictors of lung cancer mortality in this study.

Another study not part of the prior meta-analyses provides relevant information regarding the question of the relative lung cancer potency of the fibre types. Loomis *et al.* (2009) carried out a retrospective cohort mortality study of textile workers from four plants in North Carolina that had never been studied before. Workers in this cohort were primarily exposed to chrysotile asbestos that was imported from Quebec. A small amount of amosite was used in an operation in one of the plants. Overall, an excess of lung cancer was observed in this study (SMR, 1.96; 95%CI: 1.73–2.20), which was very similar in magnitude to that reported in the South Carolina cohort study of textile workers (Hein *et al.*, 2007). However, the slope for the exposure–response between asbestos exposure and lung cancer was considerably lower than that reported in the South Carolina cohort study. The reasons for these differences in the exposure–response relationships are unknown, but one possible reason may be that quality of the exposure information was superior in the South Carolina study, and that the difference could be explained by an attenuation of the slope due to exposure misclassification in Loomis *et al.* (2009).

2.2.2 Environmental exposures

Evidence of an association in women between lung cancer and environmental exposures in New Caledonia to field dust containing tremolite and the use of a whitewash ("po") containing tremolite has been reported (Luce *et al.*, 2000). A positive association with heavy residential exposure to asbestos was observed in a lung cancer case–control study the Northern Province of South Africa, which is a crocidolite and amosite mining area (Mzileni *et al.*, 1999). The association was strongest among women who resided in heavily exposed areas (odds ratio [OR], 5.4; 95%CI: 1.3–22.5; Ptrend = 0.02). A study of lung cancer mortality among women in two chrysotile mining regions of Quebec did not result in an increase in lung cancer (SMR, 0.99; 95%CI: 0.78–1.25) relative to women from 60 other areas of Canada (Camus *et al.*, 1998).

2.2.3 Non-commercial asbestiform amphibole fibres

There is emerging epidemiological evidence that non-commercial amphibole fibres that are asbestiform have carcinogenic potential. These fibres are not technically "asbestos," and they were never commercially marketed. However, the Working Group felt it was important to discuss the recent evidence concerning these

fibres because of their similarity to asbestos, and because of public concerns regarding this issue.

Several studies have described adverse health associations with the amphibole fibres that contaminated vermiculite mined in Libby, Montana, USA. These fibres were originally characterized as from the tremolite-actinolite series (IARC, 1987a), however, they have been more recently described by the US Geological Society as approximately 84% winchite, 11% richterite, and 6% tremolite (Meeker *et al.*, 2003). Sullivan (2007) reported standardized mortality ratios (SMRs), using cause of death data and expected mortality for the underlying cause of death based on national age-, race-, and sex-specific rates. Using a 15-year exposure lag, there were increased SMRs for all cancer (SMR, 1.4; 95%CI: 1.2–1.6; $n = 202$), and lung cancer (SMR, 1.7; 95%CI: 1.4–2.1; $n = 89$). Increasing risks were observed across categories of cumulative exposure; the SMR estimates were 1.5, 1.6, 1.8, and 1.9 in the 1–4.49, 4.5–22.9, 23.0–99.0, and ≥ 100 f/mL–years exposure categories, respectively. Results from other studies (Amandus *et al.*, 1987; McDonald *et al.*, 2004) of analyses using a continuous measure of exposure also resulted in statistically significant relationships with lung cancer mortality risk. For example, in the updated analysis by McDonald *et al.* (2004), the estimated linear increase in relative risk of respiratory cancer risk per 100 f/mL–years cumulative exposure was 0.36 (95%CI: 0.03–1.2; $P = 0.02$).

2.3 Mesothelioma

Pleural and peritoneal mesotheliomas are very rare malignancies that occur in the mesothelial cells that line these cavities. The first report of a possible association between asbestos exposure and mesothelioma was by Wagner *et al.* (1960) who described an outbreak of mesothelioma in a crocidolite mining region of South Africa. The majority of the cases reported had worked in the mines (23/33) but some of the cases had also occurred among individuals with no history of occupational exposures (10/33). Since then, an excess of mesothelioma has been observed in a large number of cohort and case–control studies (summarized in online Tables 2.2, 2.3 and Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.4.pdf) in a variety of different industries using and producing asbestos. Although the causal association between mesothelioma and asbestos has been well established, several important issues remain to be resolved that are discussed below.

2.3.1 Fibre type

Although all forms of asbestos can cause mesothelioma, there is considerable evidence that the potency for the induction of mesothelioma varies by fibre type, and in particular that chrysotile asbestos is less potent than amphibole forms of asbestos. An excess of mesothelioma has been reported in cohort studies of chrysotile exposed miners and millers in Quebec (Liddell *et al.*, 1997), and in South Carolina asbestos textile workers who were predominantly exposed to chrysotile asbestos imported from Quebec (Hein *et al.*, 2007). However, the fact that the chrysotile asbestos mined in Quebec is contaminated with a small percentage (< 1.0%) of amphibole (tremolite) asbestos has complicated the interpretation of these findings. McDonald *et al.* (1997) found in a nested case–control study for mesothelioma in the Thetford mines of Quebec that an association with asbestos exposure was evident in mines from a region with higher concentrations of tremolite, and not in another region with lower concentrations of tremolite. Bégin *et al.* (1992) noted that although tremolite levels may be 7.5 times higher in Thetford than in Asbestos, the incidence of mesothelioma in these two Quebec mining towns was proportional to the size of their workforce. This suggests that the tremolitic content of the ores may not be a

determinant of mesothelioma risk in Quebec. Separate analyses for workers at the Thetford and Asbestos mines and mills did not demonstrate a different exposure–response relationship for asbestos and mesothelioma in the two mining areas (McDonald & McDonald, 1995).

In a mesothelioma case–control study in South Africa, an association was reported with exposures to crocidolite and amosite asbestos, but no cases were found to have been exclusively exposed to chrysotile asbestos (Rees *et al.*, 1999). One possible explanation for these negative findings for chrysotile is that South African chrysotile asbestos may contain relatively little tremolite (Rees *et al.*, 1992). Another possible explanation is that chrysotile mining began later, and production levels were lower than in the crocidolite and amosite mines of South Africa. Cases of mesothelioma have been reported among asbestos miners in Zimbabwe, which has been reported to be uncontaminated with tremolite asbestos (Cullen & Baloyi, 1991). Excess mesothelioma mortality (standardized incidence ratio [SIR], 4.0, 95%CI: 1.5–8.7) was reported in miners and millers from a chrysotile mine in Balangero, Italy (Mirabelli *et al.*, 2008), reportedly free of amphibole contamination (Piolatto *et al.*, 1990).

An evaluation of the relative potency of the different fibre types of asbestos has been considered in the meta-analyses that were previously described (see prior section on lung cancer) by Hodgson & Darnton (2000) and Berman & Crump (2008a, b). Hodgson & Darnton (2000) used the percentage of mesothelioma deaths of all deaths expected (at an age of first exposure of 30) per unit of cumulative exposure (Rm) as the measure for their analysis. They computed separate estimates of Rm for crocidolite, amosite and chrysotile asbestos. Based on their analyses, they estimated that the ratio of the potency for mesothelioma (pleural and peritoneal combined) was 1:100:500 for chrysotile, amosite, and crocidolite respectively.

The meta-analysis conducted by Berman & Crump (2008a) was based on the analysis of the slopes (Km) that were estimated using an approach that assumes that the mortality rate from mesothelioma increases linearly with the intensity of exposure, and for a given intensity, increases indefinitely after exposure ceases, approximately as the square of time since first exposure (lagged 10 years). This model was tested with the raw data from several studies, and found to provide a good fit to the data (Berman & Crump, 2008b). Regression models were fitted to the study Km values that included information from surrogate studies to estimate fibre type (chrysotile versus amphiboles) and fibre length (short versus long) specific potency slopes (Berman & Crump, 2008a). Alternative models were fitted with exposure metrics based on different fibre widths. The hypothesis that chrysotile and amphibole forms of asbestos are equipotent was strongly rejected, and the hypothesis that potency for chrysotile asbestos was 0 could not be rejected based on their models ($P < 0.001$ and $P = 0.29$, respectively, for all-widths model). The best estimates for the relative potency of chrysotile ranged from zero to about 1/200th that of amphibole asbestos (depending on the width of the exposure metric used in the model). [The Working Group noted that there is a high degree of uncertainty concerning the accuracy of the relative potency estimates derived from the Hodgson & Darnton and Berman & Crump analyses because of the severe potential for exposure misclassification in these studies.]

Two newer studies, not part of the prior meta-analyses, provide important information regarding the question of the relative potency of the fibre types. The first is a study of a cohort of textile workers in North Carolina not previously examined (Loomis *et al.*, 2009). Workers in this cohort were primarily exposed to chrysotile asbestos imported from Quebec. A relatively large excess of both mesothelioma [SMR, 10.92; 95%CI: 2.98–27.96] and pleural cancer [SMR,

12.43; 95%CI: 3.39–31.83]. The pleural and mesothelioma deaths combined comprised 0.3% of all deaths. This percentage was nearly identical to the estimate developed for the chrysotile cohorts in a review article by Stayner *et al.* (1996). Based on the approach that Hodgson & Darnton used in their meta-analysis, the authors estimated that the percentage of deaths per unit of fibre exposure was 0.0058% per f–y/mL (0.0098% per f–y/mL for workers followed ≥ 20 years). This estimate was considerably higher than the estimate developed by Hodgson & Darnton of 0.0010% per f–yr/mL for cohorts exposed to chrysotile.

The other study investigated mesothelioma among chrysotile miners and millers, and resident communities in Balangero, Italy. The chrysotile mined at Balangero was reported to be free of tremolite and other amphiboles. The ore contains trace amounts of another fibre called blangeroite, which is not an amphibole (Turci *et al.*, 2009). A previous cohort of the miners and millers in Balangero with follow up to 1987 identified only two deaths from mesothelioma (Piolatto *et al.*, 1990). Cases of mesothelioma were identified from a local mesothelioma registry comprises people who had been mine employees; employees of subcontractors or other firms transporting or refining Balangero asbestos, asbestos ore; residents of the area who were exposed from air pollution, living with a mine employee or from mine tailings from Balangero. Six cases of mesothelioma were identified among blue-collar miners, and an estimated 1.5 deaths (SIR, 4.00; 95%CI: 1.47–8.71) would be expected based on a previous cohort study (Piolatto *et al.*, 1990), and conservative assumptions about the cohort. Additional cases of mesothelioma were identified among white-collar miners (three cases), workers in the mine hired by subcontractors (five cases), and from non-occupational exposures or exposure to re-used tailings (ten cases). Expected numbers of mesothelioma cases could not be derived for these groups because they were not part of the original cohort definition. The findings from this investigation indicate that the previous risk of mesothelioma for the Balangero cohort were seriously underestimated.

2.3.2 Fibre size

Based on a review of toxicological and human studies, Lippmann (1990) suggested that fibres shorter than 0.1 µm and longer than 5 µm are related to mesothelioma in humans. The Berman & Crump meta-analyses provided weak evidence that fibre length is a determinant of the potency of asbestos. The test of the hypothesis that long fibres (length ≥ 10 µm) and short fibres (5 < length < 10 µm) are equipotent was nearly rejected in some models (e.g. $P = 0.09$ for all widths). Thus, their findings provide weak support that long fibres may be more potent than short fibres for mesothelioma. There was little evidence in their analyses that thin fibres (width < 0.4 or < 0.2 µm) were stronger predictors of mesothelioma potency than all fibre widths combined. A major limitation of their analysis was that it relied on surrogate data to estimate the fibre-size distributions for the studies used in the meta-analysis.

2.3.3 Pleural versus peritoneal tumours

The ratio of pleural to peritoneal mesotheliomas has varied considerably in different epidemiological studies of asbestos-exposed cohorts. In the cohort studies included in the meta-analysis conducted by Hodgson & Darnton (2000), the percentage of mesotheliomas that were peritoneal varied from 0 to over 50%. Hodgson & Darnton reported that peritoneal mesotheliomas increased with the square of cumulative exposure to asbestos (i.e. a supralinear relationship); whereas pleural mesotheliomas increased less than linearly with cumulative exposure to asbestos. This implies that the number of peritoneal mesotheliomas would dramatically increase relative to the number of pleural mesotheliomas at high asbestos exposure levels. Welch *et al.*

(2005) found a strong association (OR, 5.0; 95%CI: 1.2–21.5) between asbestos exposure and peritoneal cancer in a population-based case–control study. This study included a large percentage of men with what were judged to be low exposures to asbestos.

2.3.4 Environmental exposures

An excess of mesothelioma has been observed in several studies of communities with environmental exposure to asbestos. A large excess of mesothelioma was reported in a study of people living in villages in Turkey exposed to erionite used to whitewash their homes (Baris *et al.*, 1987). An excess in mesothelioma was reported among people living near crocidolite mining regions in South Africa and Western Australia (Wagner & Pooley, 1986), among people residing in areas of tremolite contamination in Cyprus (McConnochie *et al.*, 1987) and New Caledonia (Luce *et al.*, 2000), and with non-occupational exposures in Europe (Magnani *et al.*, 2000), Italy (Magnani *et al.*, 2001), and California (Pan *et al.*, 2005).

Mesothelioma has also been reported to occur among household members of families of asbestos workers (Anderson *et al.*, 1976; Ferrante *et al.*, 2007).

2.3.5 Non-commercial asbestiform fibres

Several studies have described adverse health associations with the amphibole fibres that contaminated vermiculite mined in Libby, Montana, USA. These fibres were originally characterized as from the tremolite-actinolite series (IARC, 1987a); however, they were subsequently described by the US Geological Society as being composed of approximately 84% winchite, 11% richterite, and 6% tremolite (Meeker *et al.*, 2003). Sullivan (2007) reported SMRs, using cause of death data and expected mortality for the underlying cause of death based on national age-, race-, and sex-specific rates. Using a 15-year exposure lag, there were increased SMRs, mesothelioma defined by ICD-10 for deaths after 1999 (SMR, 14.1; 95%CI: 1.8–54.4; n = 2) and pleural cancer (SMR, 23.3; 95%CI: 6.3–59.5; n = 4). The only exposure–response modelling of mesothelioma was presented in the paper by McDonald *et al.*, based on 12 mesothelioma cases (McDonald *et al.*, 2004). Using Poisson regression, the mesothelioma mortality rate across increasing categories of exposure was compared with the rate in the lowest exposure category. For the cumulative exposure metric, the relative risk estimates were 1.0 (referent), 3.72, 3.42, and 3.68, based on 1, 4, 3, and 4, cases, respectively. The mean exposure level in these four quartiles was 8.6, 16.7, 53.2, and 393.8 f/mL–yr, respectively. It should be noted that the referent group was also at excess risk of dying from mesothelioma, i.e. there were 1–3 cases of mesothelioma observed in the referent group, which may have attenuated the observed effects.

A high incidence of mesothelioma was reported among residents of Biancavilla, Italy, a city in eastern Sicily (SMR, 7.21; 95%CI: 3.59–13.00). Reviewing of the work histories of the cases did not indicate an occupational explanation for these exposures, and thus environmental explanations for the mesothelioma excess were sought. Environmental studies have indicated that these mesotheliomas are most likely due to exposures to fluoro-edenite which is a newly recognized fibre that is very similar in morphology and composition to the tremolite-actinolite series (Comba *et al.*, 2003; Bruno *et al.*, 2006; Putzu *et al.*, 2006).

2.4 Other cancer sites

Beyond lung cancer and mesothelioma, the body of literature examining associations between asbestos and other cancers is more sparse. This reflects the fact that lung cancer and mesothelioma have been the principal areas of research

until relatively recently, and other cancers were often not considered in detail in published reports. Clinical and epidemiological studies that span the past five decades suggest, however, that asbestos may be associated with other cancers in addition to lung cancer and mesothelioma. To examine these associations in detail, the US IOM (2006) published a report evaluating the evidence relevant to causation of cancer of the pharynx, larynx, oesophagus, stomach, colon and rectum by asbestos. The present analysis draws on the IOM analysis and presents the most significant positive and negative studies for each anatomical site, with an emphasis on studies that presented data on dose–response as well as on published meta-analyses. Additionally, the present analysis examines the association between asbestos exposure and ovarian cancer, an association that was not examined by the IOM.

2.4.1 Cancer of the pharynx

See Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.5.pdf.

(a) Cohort Studies

The Working Group examined 16 cohort studies of asbestos and cancer of the pharynx. Some of these studies examined all cancers of the lips, oral cavity, and pharynx. Others restricted their examination to the pharynx itself. Two studies examined only cancers of the hypopharynx. The main findings are summarized in the following paragraphs.

Selikoff & Seidman (1991) observed an SMR for cancer of the oropharynx of 2.18 (95%CI: 1.62–2.91) among a cohort of 17800 male asbestos insulation workers across the USA and Canada. This is the cohort study with the largest number of deaths from pharyngeal cancer, a total of 48 deaths.

Piolatto *et al.* (1990) observed an SMR for cancer of the oropharynx of 2.31 (95%CI: 0.85–5.02; based on six deaths) in a cohort of 1058 asbestos miners in northern Italy exposed to chrysotile asbestos. No association was seen in this cohort between duration of occupational exposure to asbestos and risk of cancer of the pharynx.

Reid *et al.* (2004) observed an SMR for cancer of the pharynx of 1.88 (95%CI: 1.15–3.07; based on 16 deaths) in a cohort of 5685 crocidolite asbestos miners and millers in Western Australia.

Sluis-Cremer *et al.* (1992) observed an SMR for cancer of the lip, oral cavity and pharynx of 2.14 (95%CI: 1.03–3.94; based on 10 deaths) in a cohort of 7317 male asbestos miners in South Africa, some exposed to crocidolite and others to amosite. Cancer of the pharynx was defined in this population as cancer of the lip, oral cavity or pharynx. There was no excess mortality for cancer of the pharynx in the subcohort of amosite asbestos miners (SMR, 0.42; 95%CI: 0.00–1.97), but in the subcohort of crocidolite asbestos miners, the SMR for cancer of the pharynx was 2.94 (95%CI: 1.16–6.18).

Pira *et al.* (2005) observed an SMR for cancer fo the pharynx of 2.26 (95%CI: 0.90–4.65; based on seven deaths) in a cohort of 1996 workers in the asbestos textiles industry in Italy.

Other cohort studies of populations occupationally exposed to asbestos in a range of industries contained only small numbers of deaths from cancer of the pharynx (most < 10 deaths), were generally non-positive in their findings, and reported little evidence for dose–response relationships.

(b) Case–control studies

Case–control studies examining the association between asbestos exposure and cancer of the pharynx have two advantages over cohort studies:

1. they are able to collect more cases of this relatively uncommon malignancy; and
2. they are able to adjust for alcohol and tobacco consumption, the two most common causes

of cancer of the pharynx in developed and developing countries.

The present review included six case–control studies. Four of them adjusted for alcohol and tobacco consumption. The main findings are summarized in the following paragraphs.

Marchand *et al.* (2000) carried out a hospital-based, case–control study of 206 cases of cancer of the hypopharynx and 305 controls in France, and found a relative risk of 1.80 (95%CI: 1.08–2.99) in the 161 of their cases ever exposed to asbestos, adjusted for exposure to tobacco and alcohol.

Berrino *et al.* (2003) conducted a multicentre, case–control study of cancer of the hypopharynx in Europe, and found an odds ratio (OR) for "probable" exposure to asbestos of 1.8 (95%CI: 0.6–5.0). This study was restricted to analyses of cancers of the hypopharynx. For cases with "possible" exposure to asbestos, the odds ratio was 1.80 (95%CI: 0.90–3.90). These odds ratios were adjusted for exposure to tobacco and alcohol.

Zheng *et al.* (1992) conducted a population-based, case–control study of cancer of the pharynx in Shanghai, the People's Republic of China, with 204 incident cancer cases and 414 controls. The relative risk for asbestos exposure was 1.81 (95%CI: 0.91–3.60). Cigarette smoking and alcohol consumption were observed to be positively associated with cancer fo the pharynx. By contrast, increasing intake of certain fruits and vegetables, notably oranges, tangerines and Chinese white radishes, appeared to be associated with a reduced risk for cancer of the pharynx.

(c) Meta-analyses

The IOM (2006) conducted a meta-analysis of the published cohort studies examining the association between asbestos exposure and cancer of the pharynx. The IOM noted that the findings of the cohort studies were consistently positive. They calculated that the "estimated aggregated relative risk of cancer of the pharynx from any exposure to asbestos was 1.44 (95%CI: 1.04–2.00). "The IOM noted that few studies had evaluated dose–response trends, and that there was no indication of higher risks associated with more extreme exposures."

The IOM also conducted a meta-analysis of the case–control studies examining the association between asbestos exposure and cancer of the pharynx. The IOM reported the summary relative risk for cancer of the pharynx in people with "any" exposure to asbestos compared to people with no exposure to be 1.5 (95%CI: 1.1–1.7). The IOM observed that the studies were inconsistent, and that there was little evidence for a dose–response relationship.

2.4.2 Cancer of the larynx

See Table 2.5 online.

Cancer of the larynx in relation to asbestos exposure has been studied in a large number of cohort and case–control studies undertaken among occupationally exposed populations in North and South America, Europe, and Asia. (IOM, 2006).

(a) Cohort studies

Cohort studies of workers exposed occupationally to asbestos have found evidence for an association between asbestos exposure and cancer of the larynx across a broad range of industries. The Working Group reviewed 29 cohort studies encompassing 35 populations exposed to asbestos. Noteworthy findings from among these studies are summarized in the following paragraphs.

Selikoff & Seidman (1991) found an SMR for cancer of the larynx of 1.70 (95%CI: 1.01–1.69) among 17800 male insulation workers in the USA and Canada.

Musk *et al.* (2008) found an SMR for cancer of the larynx of 1.56 (95%CI: 0.83–2.67) among 6943 asbestos miners and millers from Western Australia, exposed predominantly to crocidolite

asbestos, when all cohort members lost to follow-up were assumed to be alive. When the analysis was re-run censoring all subjects at the date last know to be alive, the SMR was 2.57 (95%CI: 1.37–4.39).

Reid *et al.* (2004) carried out a study of cancer incidence in this same Australian cohort, and found a significant increase in incidence of cancer of the larynx (SIR, 1.82; 95%CI: 1.16–2.85).

Piolatto *et al.* (1990) found an SMR for cancer of the larynx of 2.67 (95%CI: 1.15–5.25; based on eight deaths) in a cohort study of 1058 male asbestos miners in northern Italy. In the subset of this cohort with > 20 years' exposure to asbestos, the SMR for cancer of the larynx was 4.55 (95%CI: 1.47–10.61). There was evidence of a positive dose–response relationship between cumulative exposure to asbestos dust, measured as fibre–years, and risk of death from cancer of the larynx. The SMRs for cancer of the larynx were 1.43 (95%CI: 0.04–7.96) in workers with exposure < 100 fibre–years; 2.22 (95%CI: 0.27–8.02) in workers with exposure of 100–400 fibre–years; and 3.85 (95%CI: 1.25–8.98) in workers with cumulative exposure > 400 fibre–years.

Peto *et al.* (1985) found an overall SMR for cancer of the larynx of 1.55 (95%CI: 0.42–3.97; based on four deaths) in a cohort of 3211 asbestos-textile workers in the United Kingdom. When workers were subdivided according to time since first employment, and by duration of employment in "scheduled" (asbestos-exposed) areas of the plant, four deaths from cancer of the larynx were observed in the most heavily exposed group versus 1.53 expected (SMR, 2.55).

Pira *et al.* (2005) found an overall SMR for cancer of the larynx of 2.38 (95%CI: 0.95–4.90; based on seven deaths–all of them in male workers) in a cohort of 889 men and 1077 women employed in an asbestos textiles plant in Italy.

Raffn *et al.* (1989) found an overall SIR for cancer of the larynx of 1.66 (95%CI: 0.91–2.78) in a cohort study of 7986 men and 584 women employed in the asbestos-cement industry in Denmark However, in the subset with > 5 years employment, the SIR was 2.27 (95%CI: 0.83–4.95), and in the group first employed from 1928–40, the SIR was 5.50 (95%CI: 1.77–12.82).

(b) Case–control studies

Case–control studies are important in examining relationships between asbestos exposure and cancer of the larynx, because they overcome the relative rarity of the diagnosis in cohort studies, and also because they permit consideration of potential confounding by exposure to tobacco and alcohol, the two most important risk-factors for this malignancy in developed and developing countries.

The Working Group analysed 15 case–control studies of asbestos and cancer of the larynx. This analysis revealed that 14 of the 15 published studies had found evidence for a significantly positive association between asbestos exposure and cancer of the larynx; only one study (Luce *et al.*, 2000) reported an odds ratio below 1.0.

(c) Meta-analyses

The IOM conducted a meta-analysis of cohort studies examining the association between asbestos exposure and cancer of the larynx. For studies examining "any" versus no exposure, the summary relative risk was 1.4 (95%CI: 1.19–1.64). For studies comparing "high" exposure versus no exposure, the lower bound summary relative risk was 2.02 (95%CI: 1.64–2.47), and the upper bound summary relative risk was 2.57 (95%CI: 1.47–4.49).

The IOM also conducted a meta-analysis of the published case–control studies examining the association between asbestos exposure and cancer of the larynx (IOM, 2006). This meta-analysis calculated a summary relative risk of 1.43 (95%CI: 1.15–1.78), before adjusting for consumption of tobacco and alcohol. After adjusting for tobacco and alcohol consumption, the association of cancer of the larynx with

asbestos exposure persisted, with an adjusted summary relative risk of 1.18 (95%CI: 1.01–1.37).

2.4.3 Cancer of the oesophagus

See Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.6.pdf.

(a) Cohort studies

The Working Group examined 25 studies of cohorts occupationally exposed to asbestos. Notable findings from among these studies are:

Selikoff & Seidman (1991) found an SMR for cancer of the oesophagus of 1.61 (95%CI: 1.13–2.40) among a cohort of 17800 asbestos insulations workers across the USA and Canada. Selikoff & Seidman (1991) observed that cancer in asbestos workers is "very much related to latency," with most of the increased risk occurring only 25 or more years from the onset of occupational exposure to asbestos.

In a cohort of 10939 male and 440 female asbestos miners and millers in Quebec, Canada, exposed predominantly to chrysotile asbestos, followed through 1975, McDonald *et al.* (1980) reported that mortality for cancer of the oesophagus and stomach (the two were combined) was elevated (SMR, 1.27). Further follow-up through 1988 of a subset of this cohort, consisting of 5335 men, examined esophageal cancer mortality separate from stomach cance,r and found no excess mortality (SMR, 0.73; 95%CI: 0.35 – 1.34) (McDonald *et al.*, 1993).

Musk *et al.* (2008) found an SMR for cancer of the oesophagus was 1.01 (95%CI: 0.71–1.40) in a cohort study of 6943 asbestos miners from Western Australia followed through 2000, exposed predominantly to crocidolite asbestos, when all cohort members lost to follow-up were assumed to be alive. When the analysis was re-run censoring all subjects at the date last known to be alive, the SMR was 1.20 (95%CI: 0.62–2.10).

Hein *et al.* (2007) found an SMR for cancer of the oesophagus of 1.87 (95%CI: 1.09–2.99) in a cohort of 3072 asbestos textile workers in South Carolina, occupationally exposed to chrysotile asbestos and followed through 2001.

Peto *et al.* (1985) found 11 deaths from cancer of the oesophagus versus 6.59 expected (SMR = 1.67; 95%CI: 0.83–2.99) in a cohort of 3211 male asbestos textile workers in the United Kingdom. For the subset of workers with 10+ years employment in "scheduled" (asbestos-exposed) areas of the plant and with 20+ years since first employment, the SMR for cancer of the oesophagus was 2.36 (95%CI: 0.49–6.91). For all workers in this cohort with < 20 years since first employment, two deaths for cancer of the oesophagus was observed versus 2.18 expected, and for workers with 20+ years since first employment, there were nine deaths from cancer of the oesophagus versus 4.4 expected (see Table 6 in Peto *et al.*, 1985).

Berry *et al.* (2000) found a 2-fold excess mortality for cancer of the oesophagus (SMR, 2.08; 95%CI: 1.07–3.63) among a cohort of over 5000 asbestos-exposed factory workers in the east end of London, United Kingdom, who had produced asbestos insulation boards, and who were followed for 30+ years. In the subset of workers within this population with "severe" asbestos exposure of more than 2 years' duration, the SMR for cancer of the oesophagus was 5.62 (95%CI: 1.82 – 13.11). And in the subset of women with "severe" exposure to asbestos of > 2 years, the SMR for cancer of the oesophagus was 9.09 (95%CI: 1.10–32.82).

Other cohort studies of various groups occupationally exposed to asbestos – asbestos-cement workers, friction products workers, and "generic" asbestos workers – yield generally non-positive results for cancer of the oesophagus.

(b) Case–control studies

The Working Group examined five case–control studies that examined the association between asbestos exposure and cancer of the oesophagus.

A case–control study in Quebec, Canada found an OR of 2.0 (95%CI: 1.1–3.8) for any exposure to asbestos among 17 patients diagnosed with squamous cell carcinoma of the oesophagus. (Parent *et al.*, 2000).

A case–control study conducted within a cohort of nearly 400000 Swedish construction workers found evidence for a positive association between asbestos exposure and adenocarcinoma of the oesophagus. Relative risk increased from 1.0 (reference) among workers with no asbestos exposure, to 1.7 (95%CI: 0.5–5.4) among those with "moderate" exposure, and to 4.5 (95%CI: 1.4–14.3) among those workers with "high" asbestos exposure, thus suggesting a positive dose–response relationship (Jansson *et al.*, 2005).

(c) Meta-analyses

Meta-analyses have been undertaken of the association between asbestos exposure and cancer of the oesophagus:

A meta-analysis by Frumkin & Berlin (1988) stratified studies according to SMR for lung cancer and also according to the percentage of deaths due to mesothelioma. The rationale is that a higher death rate for either lung cancer or mesothelioma is taken to be a surrogate index of higher cumulative exposure to asbestos. However, no association was observed between death rate for cancer of the oesophagus in the published cohorts by either lung cancer SMR or percentage of death for mesothelioma.

Meta-analyses by Edelman (1988) and by Goodman *et al.* (1999) did not detect an association between asbestos exposure and cancer of the oesophagus.

A meta-analysis by Morgan *et al.* (1985) that examined earlier studies, which tended to have heavier exposure, found a summary SMR for cancer of the oesophagus in asbestos-exposed workers of 2.14 (95%CI: 1.326–3.276). When cases of cancer of the oesophagus based on "best evidence" (pathological review) were deleted from these cohorts, the SMR remained elevated at 2.38 (95%CI: 1.45–3.68).

The IOM (2006) conducted a meta analysis of 25 cohort studies and reported a summary relative risk of 0.99 (95%CI: 0.78–1.27) for any exposure to asbestos versus no exposure. The IOM also examined the relative risk of "high" versus no exposure, and calculated a lower bound summary relative risk of 1.35 (95%CI: 0.81–2.27), and a higher bound summary relative risk of 1.43 (95%CI: 0.79–2.58). The IOM determined that there were too few case–control studies to permit a meta-analysis.

2.4.4 Cancer of the stomach

The Working Group reviewed 42 cohort studies and five population-based case–control studies that examined the association between asbestos and cancer of the stomach (See Table 2.6 online).

(a) Cohort studies

Notable findings among the cohort studies are:

Selikoff *et al.* (1964) reported a nearly 3-fold excess mortality for cancer of the stomach (12 observed versus 4.3 expected) in a population of 632 insulation workers in New York and New Jersey occupationally exposed to asbestos dust. Further analysis within this cohort (Selikoff *et al.*, 1979) found evidence of a dose–response relationship between duration of exposure to asbestos (in years), and risk of death from cancer of the stomach. The SMR for cancer of the stomach increased from 0.00 in workers exposed for < 20 years, to 4.00 (95%CI: 1.47 – 8.71) in those exposed for 20 –35 years, and to 3.42 (95%CI: 1.82 – 5.85) in those exposed for > 35 years.

Selikoff *et al.* (1967) found a modest, non-significant increase in risk of death for cancer of the stomach: 34 observed v. 29.4 expected, (SMR = 1.16;95%CI: 0.92 – 1.78) in a larger cohort study of 17800 insulation workers across the USA and Canada. No data on dose–response for cancer of the stomach were presented in this analysis.

Liddell *et al.* (1997) reported an overall SMR for cancer of the stomach of 1.24 (95%CI: 1.07 –1.48) in a study of 10918 asbestos miners and millers exposed predominantly to chrysotile asbestos, in Quebec, Canada. Within this cohort, a positive dose–response relationship was observed between cumulative exposure to asbestos dust (mcpf-year) and mortality for cancer of the stomach. Thus, for workers with cumulative dust exposure < 300, the SMR was 1.16; for workers with cumulative exposure of 300 – 400, the SMR was 1.29; for workers with cumulative exposure of 400 – 1000, the SMR was 1.21; and for workers in the highest exposure category, with cumulative exposure > 1000, the SMR was 3.21 (95%CI: 1.87 –5.14). An additional finding in this cohort was a modest interaction between cumulative asbestos exposure, cigarette smoking, and mortality from cancer of the stomach.

Musk *et al.* (2008) found an SMR for cancer of the stomach of 1.01 (95%CI: 0.71 – 1.40) in a cohort of 6943 asbestos miners and millers exposed predominantly to crocidolite asbestos in Wittenoom, Western Australia, followed through the end of 2000, and when all cohort members lost to follow-up were assumed to be alive. When the analysis was re-run censoring subjects at the date last known to be alive, the SMR was 1.71 (95%CI: 1.20–2.35).

Reid *et al.* (2004) conducted a nested case–control study within this same Australian cohort, and found a positive exposure-response relationship between cancer of the stomach and cumulative exposure to asbestos (test for trend, $P = 0.057$). No association was seen between cancer of the stomach and either time since first exposure or year of starting work with asbestos. Smoking status was associated with cancer of the stomach, but not significantly.

Meurman *et al.* (1974) found a non-significant increase in SMR for cancer of the stomach: SMR = 1.42 (95%CI: 0.76 – 2.43) in a cohort of 736 asbestos miners in Finland exposed to anthophyllite asbestos.

Berry *et al.* (2000) found a modest, non-significant increased risk for death from cancer of the stomach: 28 observed versus 23.1 expected (SMR, 1.21; 95%CI: 0.81–1.75) in a British study of factory workers producing asbestos insulation in the east end of London.

Strongly positive dose–response associations between cumulative asbestos response and cancer of the stomach were observed in two cohort studies of Chinese factory workers – one in Beijing and the other in Qingdao; relative risks for cancer of the stomach were 4.4 and 2.4, respectively (Zhu & Wang, 1993; Pang *et al.*, 1997).

Raffn *et al.* (1989) observed 43 deaths from cancer of the stomach versus 30.09 expected (SMR, 1.43; 95%CI: 1.03 – 1.93) in a cohort of 7986 men employed from 1928–84 in the asbestos cement industry in Denmark.

Enterline *et al.* (1987) observed a SMR for cancer of the stomach of 1.80 (95%CI: 1.10–2.78) in a cohort of 1074 retired US asbestos workers.

Epidemiological studies of cohorts with asbestos-related diseases – asbestosis and benign pleural disease – have not found increased mortality for cancer of the stomach (Germani *et al.*, 1999; Karjalainen *et al.*, 1999; Szeszenia-Dabrowska *et al.*, 2002).

(b) Case–control studies

Case–control studies exploring the relationship between asbestos exposure and cancer of the stomach yield inconsistent results. The Working Group reviewed five case–control studies. Notable findings are these:

A study from Poland (Krstev *et al.*, 2005) found an OR for cancer of the stomach of 1.5 (95%CI: 0.9–2.4) for workers ever exposed to asbestos, and of 1.2 (95%CI: 0.6–2.3) for workers with 10 or more years of exposure to asbestos.

The largest case–control study to examine the association between asbestos and cancer of the stomach (Cocco *et al.*, 1994) reported an odds ratio of 0.7 (95%CI: 0.5–1.1) for workers ever exposed to asbestos, and of 1.4 (95%CI: 0.6–3.0) for those with 21+ years of exposure to asbestos.

The most strongly positive case–control study linking asbestos to cancer of the stomach is the case–control study, cited above, nested within the Western Australia mining cohort (Reid *et al.*, 2004).

(c) Meta-analyses

Several meta-analyses have been undertaken of the association between asbestos exposure and cancer of the stomach.

A meta-analysis by Frumkin & Berlin (1988) stratified studies according to SMR for lung cancer and also according to percentage of deaths due to mesothelioma. Frumkin & Berlin found in cohorts where the SMR for lung cancer was < 2.00 that the SMR for cancer of the stomach was 0.91 (95%CI: 0.71–1.16). By contrast, when the SMR for lung cancer was > 2.00, the SMR for cancer of the stomach increased to 1.34 (95%CI: 1.07–1.67).

Gamble (2008) reported that point estimates for cancer of the stomach mortality tended towards 1.0 when the excess risk for lung cancer were less than 4-fold, but "tended to be somewhat elevated when lung cancer relative risks were 4-fold or greater." Gamble observed further that "combined relative risks for cancer of the stomach stratified by lung cancer categories showed a suggestive trend, with a significant deficit (0.80) when lung cancer SMRs were <1.0 that increased monotonically to a significant 1.43-fold excess in the studies with lung cancer SMRs > 3.0." Gamble observed no trend for increasing SMR for cancer of the stomach with increasing percentage of deaths from mesothelioma (Gamble, 2008).

The IOM (2006) conducted a meta-analysis of 42 cohort studies examining the association between asbestos exposure and cancer of the stomach. The IOM noted that the "majority of cohort relative risk estimates for cancer of the stomach exceed the null value (1.0), indicating excesses, although estimates varied considerably in strength." In cohorts that compared "any" versus no exposure, the summary relative risk was 1.17 (95%CI: 1.07–1.28). The IOM notes that with respect to dose–response, the summary estimates were stable. Thus in the cohorts that compared "high" versus no exposure, the lower bound summary relative risk was 1.31 (95%CI: 0.97–1.76), and the higher bound summary relative risk, 1.33 (95%CI: 0.98–1.79).

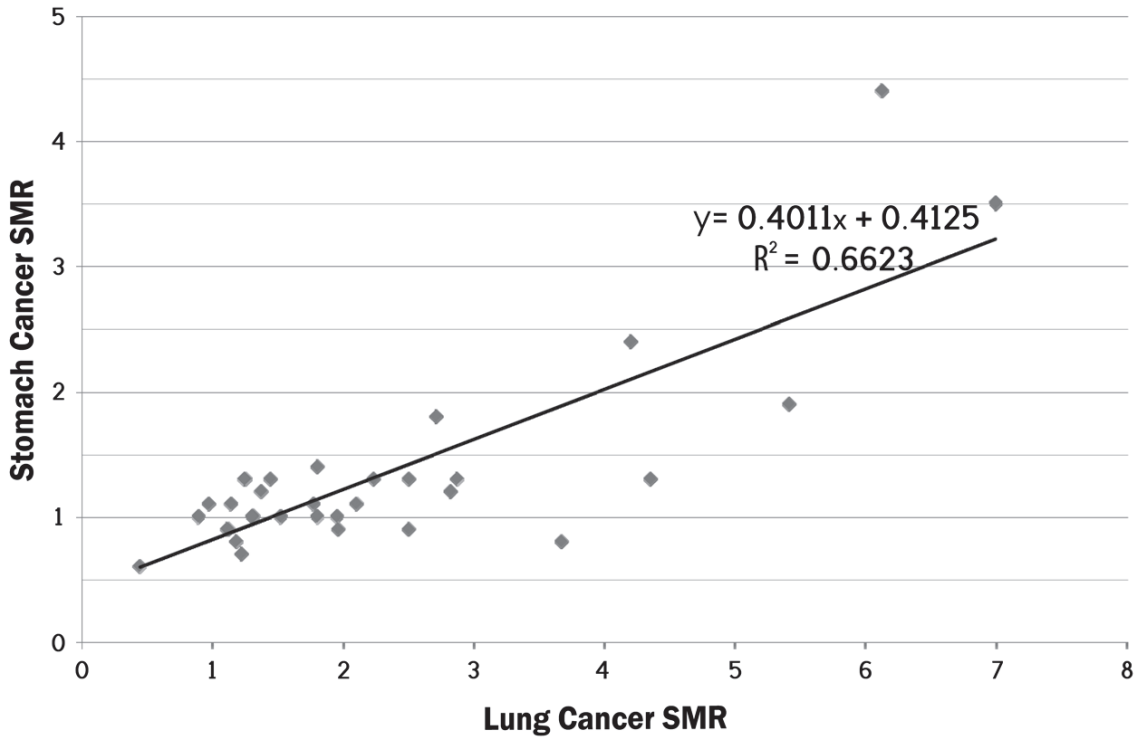
The IOM conducted a meta-analysis of the five case–control studies resulting in a combined relative risk of 1.11 (95%CI: 0.76–1.64). The summary odds ratio increased when only extreme exposure was considered (OR, 1.42; 95%CI: 0.92–2.20)

The Working Group developed a scatter plot comparing SMRs for lung cancer with SMRs for cancer of the stomach in the same cohorts. A positive trend was observed between the two, and the correlation coefficient (r2) = 0.66, see Fig. 2.1.

(i) Asbestos in drinking-water and cancer of the stomach

Ecological correlational studies conducted from the 1960s into the early 1980s suggested an association between asbestos in drinking-water and cancer of the stomach. These studies correlated population exposure to asbestos in water supplies with population cancer rates. Levy *et al.* (1976) reported an excess in cancer of the stomach among persons in Duluth, MN, USA exposed to taconite asbestos in drinking-water. Wigle (1977) saw an excess of male cancer of the stomach among some exposed to asbestos in drinking-water in Quebec. Conforti *et al.* (1981)

Fig 2.1 Stomach & lung cancer correlation in asbestos cohorts



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saw a similar association in the San Francisco Bay area, USA. Polissar *et al.* (1982) examined cancer incidence and mortality among residents of the Puget Sound area, USA, in relation to asbestos in regional drinking-water. They observed no association between asbestos exposure and cancer of the stomach. A similarly negative study was observed in a study conducted in Woodstock, NY, USA (Howe *et al.*, 1989).

Kjærheim *et al.* (2005) examined cancer of the stomach incidence in Norwegian light-house keepers exposed to asbestos in drinking-water. They found an SIR for cancer of the stomach in the entire cohort of 1.6 (95%CI: 1.0–2.3). In the subcohort with "definite" exposure to asbestos, the SIR was 2.5 (95%CI: 0.9–5.5). In those members of the definite exposure subcohort followed for 20+ years, the SIR was 1.7 (95%CI: 1.1–2.7).

Cantor (1997) conducted a systematic review of the epidemiological literature on exposure to asbestos in drinking-water and cancer of the stomach, and concluded that the available data were inadequate to evaluate the cancer risk of asbestos in drinking-water.

Marsh (1983) conducted a critical analysis of 13 epidemiological studies of asbestos and drinking-water conducted in the USA and Canada, and found no consistent pattern of association.